GENETIC AND ENVIRONMENTAL CONTRIBUTIONS TO PERSONALITY DISORDERS, LONG-TERM SICK LEAVE AND DISABILITY PENSION

A population-based twin study

Line C. Gjerde

Division of Mental Health, Department of Genetics, Environment and Mental Health
Norwegian Institute of Public Health

Submitted for the degree of PhD at the
Department of Psychology, Faculty of Social Sciences, University of Oslo

Series of dissertations submitted to the
Faculty of Social Sciences, University of Oslo
No. 453

ISSN 1504-3991

Cover: Inger Sandved Anfinsen.
Printed in Norway: AIT Oslo AS.

Produced in co-operation with Akademika publishing, Oslo.
The thesis is produced by Akademika publishing merely in connection with the thesis defence. Kindly direct all inquiries regarding the thesis to the copyright holder or the unit which grants the doctorate.

LIST OF ABBREVIATIONS

A – additive genetic effects

AIC – Akaike Information Criterion

APA – the American Psychiatric Association

AVPD – avoidant personality disorder

C – shared (common) environmental effects

CI – confidence interval

D – dominance effects

DAPP-DQ – the Dimensional Assessment of Personality Problems – Differential Questionnaire

DEPD – dependent personality disorder

DNA – deoxyribonucleic acid

DP – disability pension

DPQ – the Dysfunctional Personality Questionnaire

DSM – the Diagnostic and Statistical Manual

DZ – dizygotic twins

E – unique environmental effects

EEA – the equal environment assumption

FD-trygd – Forløpsdatabasen Trygd (the historical-event database)

FIML – full information maximum likelihood

GDP – gross domestic product

GEE – generalized estimating equations

GxE – gene-environment interaction

ICD – International Classification of Disease

LL – log likelihood

LTSL – long-term sick leave

MBR – the Medical Birth Registry

ML – maximum likelihood

MZ – monozygotic twins

NIPH – The Norwegian Institute of Public Health

NIPHTP – The Norwegian Institute of Public Health Twin Panel

NUDB – the Norwegian National Education Database

OR – odds ratio

OECD – Organization for Economic Co-operation and Development

PAWS – Predictive Analytics Software Statistics

PD – personality disorder

Q2 – second questionnaire (1998)

R – refers to the R-Project: a free software environment for statistical computing and graphics

r_{GE} – gene-environment correlation

SEM – structural equation modeling

SIDP-IV – the Structured Interview for DSM-IV Personality

SPSS – see PAWS

UK – United Kingdom

USA – United States of America

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

The project that this thesis is based on was conducted at the Norwegian Institute of Public Health (NIPH), and funded by grants from the Research Council of Norway.

When I started at NIPH, I was privileged to come to a set table regarding datasets. The datasets that I have based my work on originate from the Norwegian Institute of Public Health Twin Panel data that were later linked to the historical-event database (FD-Trygd). I would like to thank the many people who have worked hard to plan and collect these data, and those who made the linkage of the data possible. I am also very grateful to the twins for their participation.

For my time as a PhD candidate, I was provided with a team of three excellent supervisors: Ragnhild Ørstavik, Espen Røysamb and Gun Peggy Knudsen, and I have enjoyed working with all of them. Ragnhild: as my main supervisor it is almost needless to say that you have been very important for this thesis. With your research experience, writing skills, and superfast responses to the endless number of emails I have sent, you have guided me safely through this thesis. I am also very grateful for all the encouragement you have given me, and for not agreeing with me when I felt stupid. Espen: With the exception of your busy schedule and ninja hiding skills, you are the best supervisor one can have. Your statistical skills, enthusiasm and pedagogic talent have been extremely valuable to me. I am also very grateful that you opened my eyes to the possibility of becoming a PhD student when you were supervisor on my master's thesis. Gun Peggy: Your skills at handling data and your hawk's eye for details are impressive. Thanks for supporting me, for answering all kinds of more or less silly questions about SPSS (and not least all the tricky ones), and for everything else you have taught me. The NIPH is lucky to have such talented researchers.

Special thanks go to Ted Reichborn-Kjennerud, who is PI on the project I have worked on, for making this work possible. Ted has also been a valuable co-author and a competent manager of the Department of Genetics, Environment and Mental Health. Thanks also to Arne Holte and Ellinor Major for excellent leadership of the division, and to Martin Mydske Nilsen and Kari Voll for making this a wonderful place to work and for the help they have provided during my time as a PhD student.

In 2012, I spent 5 months at the Virginia Institute for Psychiatric and Behavioral Genetics working on my thesis. I would like to thank Kenneth S. Kendler for valuable supervision and for all he has taught me about twin studies. Professor Kendler is an outstanding researcher and inspirational person, and I am grateful that he would spend time supervising me. Thanks also to Steven H. Aggen and Nathan Gillespie for all the help, support and methodological guidance they provided me with during my stay.

I would also like to thank Nikolai Czajkowski for his help and considerable patience. Although he has not officially been a supervisor, I feel almost as indebted to him as I do to my other supervisors. He has taught me so much about twin modeling and statistics in general, and for that I am very grateful.

I have had the pleasure of working with a lot of people who have been my co-authors on the papers in this thesis. Those who have not already been thanked are Kristian Tambs (who was co- supervisor on my master's thesis, and also helped me find my way to NIPH), Svenn Torgersen and John Myers. Thank you for your contributions.

Fartein Ask Torvik and Kristian Østby also deserve to be thanked as they have endured countless lunches with me, and have been important PhD-student fellow accomplices. Kristian has also been a valuable co-author. We have discussed research and other important and not so important aspects of life, and it has been both fun and enlightening. Many more PhD students and post docs have also contributed to making NIPH a great place to work, and they all deserve thanks, but I will not mention names as I will most probably forget someone.

I would like to express my gratitude to my family, especially my parents, Reidunn and Sven Inge. You have encouraged me to pursue my academic interests since I was very young. Thank you for believing in me, and for always being supportive. My brothers Jarle and Morten have taught me the art of endurance through all the games and competitions we arranged when we were kids. I believe this has been a key skill for being able to complete a PhD.

My gratitude also extends to all my friends, and especially Pernille, Mari, Line Johanna, Karina, Hanna, Merethe and Nina, for helping me to not forget that there is a life outside of the office, for all the laughs and fun we have had, and for hanging in there when I complained (or boasted) about how hard (or fantastic) it is to write a PhD thesis.

Last but not least I would like to thank Jarle for all his help and support during the final stages of this thesis. Thanks for cooking me nice dinners, cheering me up and for being the awesome person that you are.

Oslo, December 2013
Line C. Gjerde

ABSTRACT

In this thesis we applied various twin models on a population-based sample of young adult Norwegian twins to investigate genetic and environmental contributions to a selection of dimensional representations of DSM-IV personality disorders (PDs), long-term sick leave (LTSL) and disability pension (DP). We also investigated to what extent LTSL and DP, as well as LTSL and a selection of PDs, share genetic and environmental risk factors in common.

Knowledge of the heritability of DSM-IV cluster C PDs corrected for measurement error has been lacking. In Paper 1, we investigated genetic and environmental contributions to dimensional representations of DSM-IV avoidant and dependent PD, using both a semi-structured interview and a self-report questionnaire conducted at a different time-point. The heritability for both PDs was in the upper range of what has previously been found. No evidence of shared environmental effects or sex differences was found for these PDs. The results further indicated that the interview measure had higher specificity for the genetic liability to these PDs than the questionnaire measure.

Few studies have investigated the heritability of LTSL and DP, and none has used a genetically informative design to investigate the structure of common and specific genetic and environmental contributions to these phenotypes. In Paper 2, we found substantial heritability for LTSL and DP. The genetic and environmental risk factors for LTSL and DP were mainly overlapping, but we also found evidence for a genetic factor of moderate size that was not shared in common between them. The specific genetic factor, as well as extreme scores on the shared genetic factor, may explain why some progress from LTSL to DP. We did not find evidence for sex differences, shared environmental effects or sibling interaction. These results indicate that familial transmission of these phenomena is mainly due to genetic factors.

The association between PDs and LTSL has been largely unexplored, and no studies have investigated the association with a genetically informative design. In Paper 3, we found that dimensional representations of DSM-IV schizotypal, paranoid and borderline PD were uniquely and significantly associated with LTSL. Subsequent twin models showed that the association between these PDs and LTSL was almost entirely due to genetic factors shared in common between the phenotypes. Genetic contributions to the selected PDs accounted for 20% of the heritability of LTSL. The results indicated that the association between PDs and LTSL was non-causal and probably due to genetic confounding, although the design we used was not sufficient for firm conclusions to be drawn on this matter.

LIST OF PAPERS

Paper 1

Gjerde, L. C., Czajkowski, N., Røysamb, E., Ørstavik, R. E., Knudsen, G. P., Østby, K., Torgersen, S., Myers, J., Kendler, K. S. & Reichborn-Kjennerud, T. (2012). The heritability of avoidant and dependent personality disorder assessed by personal interview and questionnaire. *Acta Psychiatrica Scandinavica* **126**, 448-457.

Paper 2

Gjerde, L. C., Knudsen, G. P., Czajkowski, N., Gillespie, N., Aggen, S. H., Røysamb, E., Reichborn-Kjennerud, T., Tambs, K., Kendler, K. S. & Ørstavik, R. E. (2013). Genetic and environmental contributions to long-term sick leave and disability pension: a population-based study of young adult Norwegian twins. *Twin Research and Human Genetics* **16,** 759-766.

Paper 3

Gjerde, L. C., Røysamb, E., Czajkowski, N., Knudsen, G. P., Østby, K., Tambs, K., Kendler, K. S., Reichborn-Kjennerud, T., & Ørstavik, R. E. (in press). Personality disorders and long-term sick leave: a population-based study of young adult Norwegian twins. *Twin Research and Human Genetics*.

1. INTRODUCTION

Twin studies have traditionally been used to investigate the heritability of mental and somatic disorders and various behavioral traits. During the last three to four decades such studies have provided important insights into the causes of individual variation (Plomin et al., 2001). As it has now been more or less established to what extent genetic and environmental factors contribute to variation in most mental disorders, twin studies have moved on to investigate more challenging questions, such as why phenotypes tend to co-occur, and to what extent genetic and environmental influences can account for stability and change. More recently, twin methodology has also been used to investigate phenotypes traditionally studied within the social sciences, such as life events and different types of medical benefits, as much less is known about the causes of individual variation in these phenomena.

Some individuals find it hard to function at work due to disease, illness or injuries. Although a medical disorder has to be present for an individual to be granted sick leave benefits or disability pension, it is well known that medical benefits are also dependent on an array of individual, social and work related factors. Outcomes such as sick leave and disability pension have negative consequences for the individuals and their families, as well as for society in general. It is therefore important to increase knowledge on these phenomena. Mental disorders are to date one of the most common reasons for sick leave and disability pension (Vaez et al., 2007). As modern work life is highly dependent on the ability to collaborate and interact with others, it may be difficult for individuals with mental disorders, and particularly for those with a personality disorder or certain personality disorder traits to function at work. Personality disorders and the consequences these have on work functioning are less studied than for other mental disorders. This thesis is an attempt to increase the knowledge on these subjects.

1.1 Quantitative genetics and genetic epidemiology

Psychology is a scientific discipline that spans a large number of sub-disciplines. Despite being a rather new science, compared to more established fields such as physics and mathematics, it has radically changed the way we think about ourselves and human behavior. One of the most controversial and important discoveries made in psychology is the acknowledgement of how important genes and genetic influences are for explaining variation in human behavior. The first successful studies of genetics have origins back to the 1850s, when Gregor Mendel (1822-1884) studied qualitative (either-or) traits caused by single genes in pea plants to understand the laws of

inheritance. At about the same time, Francis Galton (1822-1911) made important contributions to the scientific study of individual differences and family resemblance. The Mendelian laws and Galton's theories of inheritance were in the mid-twentieth century developed further by Karl Pearson (1857-1936) and, most successfully, by Ronald Fisher (1890-1962) to also apply to polygenic inheritance, frequently referred to as quantitative genetics or behavioral genetics. This was an important step forward, as most psychological traits have much more complicated patterns of inheritance than the single-gene traits observed in pea plants. The essence of quantitative genetics is that complex traits are influenced by many genes and that each gene is inherited according to Mendel's laws (Plomin et al., 2001). The discovery made by Watson and Crick of the molecular structure of the DNA in 1953 paved the way for gene finding studies and molecular genetics that have developed in parallel to quantitative genetics. These are, however, not within the scope of the present thesis.

Within the field of quantitative genetics we seek to analyze the mechanisms that underlie complex behavioral traits to identify the relative genetic and environmental contributions. For this purpose, various types of twin, family and adoption designs are used. During the last half-century, there has been a spectacular development in this field, and several key discoveries have been made. Most importantly, the old debate on "nature or nurture" has settled, as it has been established that individual differences in behavioral traits result from a complicated interplay of both genes and environment.

Epidemiology is defined as the study of the distribution and determinants of health related states or events in populations (WHO, 2013). Since the early origins of epidemiology, dating back to the 17th century in England (Susser & Bresnahan, 2001), the field has moved through different phases from detecting and fighting infections to a wider perspective on general health determinants and development of new methods of causal inference (Morabia, 2011). As causal inference is dependent on complex methodological designs, modern epidemiology is predominantly oriented towards identifying risk factors for diseases, an approach susceptible to confounding (Smith & Phillips, 1992). Genetic epidemiology emerged in the 1980s and is the study of genetic and environmental factors on measures of health and disease in human populations (Khoury et al., 1993; Teare, 2011). This field brought together methodologies from quantitative genetics and traditional epidemiology, and has the advantage of being able to delineate the effects of genes and environment on the phenotypes of interest.

The present thesis applies quantitative genetic methodology in the form of twin studies to illuminate different research questions. There will be much focus on the relative contributions from genetic and environmental influences on the phenotypes we have studied, and thus the

concept of genes and the environment and how they are defined within the field of behavior genetics need an introduction.

1.1.1 The environment in twin studies

It is difficult to grasp exactly what the "environment" constitutes as it may amount to almost everything that affects an individual from the outside. In the field of behavioral genetics, it is common to divide environmental factors into what makes twins in a pair more similar to each other (shared environmental factors), and what makes them different from each other (non-shared environmental factors). Shared environmental factors, often referred to as C, are those experiences and influences that are usually shared between twins and could for instance include parental rearing styles, social class, and even the intrauterine environment (Kendler & Prescott, 2006). That both twins experience the same environmental factor, such as their parents splitting up, does not, however, necessarily constitute a shared environmental influence. This happening can only be ascribed as a shared environmental influence if both twins react to it the same way and as a consequence become more equal to each other. Non-shared environmental factors, abbreviated E, are influences and experiences that are often not shared between twins in a pair, such as the influences of friends, education and marriage. If two twins experience the same environmental influence, such as their parent's divorce, but react differently to it, this would in behavioral genetic terminology be a non-shared environmental effect. It should be noted that the shared and non-shared environment are rarely measured directly, but are instead inferred through the patterns of covariation between twins. In twin models (explained under 1.1.3), E also includes measurement error.

Most twin studies find that non-shared environmental influences are more important for explaining variation in psychological traits in adults than shared environmental influences (Turkheimer, 2000). This finding may to some extent be explained by a lack of statistical power. The sample size needed to reject a twin model including additive genetic effects (explained under 1.1.2) when only shared and non-shared environmental effects are present is very high, and particularly so when the trait is binary (M. C. Neale et al., 1994). Also, the failure to detect shared environmental effects does not necessarily indicate that these effects are not important. For instance, it was found that for adoptive children, shared environmental influences had an effect on the children's overall level of IQ, but did not change individual differences (Duyme et al., 1999). In such cases, the effect would not show up in twin model estimates as a shared environmental effect. To avoid confusion about the importance of shared environment, it is useful to divide the effects into what is *objective* and what is *effective* (Kendler & Prescott, 2006). If a shared

environmental source rendered twins in a pair to be more different from each other, then that shared environment had an actual (objective) influence. However, as twin models only estimate the effects the environment has on covariance, this shared environmental influence would result in a non-shared effect, that is – the twins effectively became more different from each other.

1.1.2 Genetic effects and the concept of heritability

The basis of heredity lies in the DNA (deoxyribonucleic acid) molecules. The DNA molecule has the shape of a double helix, and is contained in the chromosomes located in the nucleus of the cells of living organisms. The double helix consists of nucleotide units composed of the nitrogenous bases guanine, adenine, thymine and cytosine. These bases are organized in pairs and held together by a backbone of sugar and phosphate. A gene can be defined as a molecular unit of heredity, and is a region of the DNA that contains the information needed to produce polypeptides, the building blocks of proteins. The gene's location on a chromosome is referred to as its locus. Alleles are alternate forms of genes, placed on the same locus on a chromosome. Diploid organisms, such as humans, have two sets of chromosomes, one set inherited from each parent. A genotype is usually defined as an individual's set of alleles, which together constitute the genetic potential, whereas a phenotype is the expressed trait that is caused by the effects of an individual's genotype and environment.

Few of the phenotypes of interest in psychology are caused by the influence of a single gene. Instead, they result from the effects of several genes (as well as environmental influences), and are thus referred to as complex or polygenic phenotypes. The genetic effects on a phenotype can be partitioned into those that are additive and those that are non-additive. The total genetic effect from additive genetic influences is simply the sum of the individual contributions. Additive genetic effects are usually referred to as A. If a parent has one copy of the allele there is a 50% chance that the offspring will inherit this allele. If the allele is inherited, its effect on the phenotype will contribute the same amount as the parents' allele did to the phenotype, and thus lead to parent-offspring similarity (Plomin et al., 2001). Non-additive genetic effects that are common to consider in behavioral genetic studies are dominance and epistasis. Dominance effects (D) imply that there is interaction between alleles at the same locus. Inherent in D is also epistasis, which imply that alleles at different loci interact (Rutter, 2006). The total genetic effects on a phenotype consist of all the additive and non-additive effects from the different loci involved.

In quantitative genetics, variance in a phenotype is assumed to arise from the combined effects of A, D, C and E. The total variance in a phenotype (P) can thus be written as follows:

$$Var(P) = Var\ (A + D + C + E)$$

However, as the statistical power needed to detect D effects is high, it is often assumed that only A contributes to the genetic effects in a phenotype (as under 5.1.4). This variance can be decomposed into the following sums, where the covariance between the elements is also taken into account:

$$Var(P) = Var(A) + Var(C) + Var(E) + 2Cov(A, C) + 2Cov(A, E) + 2Cov(C, E)$$

This expression can be simplified, as it is assumed that A and E as well as A and C are uncorrelated (as explained under 5.1.4). C and E are further uncorrelated by definition. The expected phenotypic variance is thus the sum of only three sources of variance:

$$Var(P) = Var(A) + Var(C) + Var(E)$$

In order to quantify to what extent these sources of variance contribute to a phenotype, one can compare the covariance between different types of relatives. Various types of twin and family studies are widely used in behavior genetics for this purpose. In the classical twin study, as used in the present thesis, we compare the similarity of two types of twins; monozygotic (MZ) and dizygotic (DZ) twins. MZ twinning is assumed to be a random event (Benirschke, 2009) and is still considered a biological mystery (Kendler & Prescott, 2006). It occurs when a single egg cell, fertilized by a single sperm cell, divides and develops into two genetically similar embryos during the first two weeks after fertilization. DZ twinning is the result when two egg cells are fertilized by two different sperm cells. The incidence of DZ twinning is influenced by various maternal factors, both genetic and environmental, and is found to vary across populations (Painter et al., 2006). DZ twins resemble ordinary siblings in that they share on average 50% of their genetic material, but unlike ordinary siblings they also share the intrauterine environment. Given that MZ and DZ twin grow up in the same family at the same time, they are assumed to share the family environment to an equal extent, as discussed in more detail under 5.1.4. The expected covariation between these two types of twins for a given phenotype can therefore be written as follows:

$$Cov_{MZ}(P) = Var(A) + Var(C)$$

$$Cov_{DZ}(P) = \frac{1}{2} Var(A) + Var(C)$$

These formulas indicate that if MZ twins are more similar on a phenotype than DZ twins, this must be due to them sharing more of their genetic material. To what extent genetic influences contribute to variance in a trait can be quantified with the heritability coefficient.

Heritability

Heritability is usually defined as the proportion of variance in a phenotype attributed to the genetic variance in a population at a given time. It is important to stress that a heritability coefficient is a relative size, and hence is determined by both "nature" and "nurture". This implies that the coefficient will vary with the heterogeneity or homogeneity of both the environment and the genetic composition in a population (Tesser, 1993). With no environmental variation in a population, all of the variation must be attributed to genes, which would give rise to a heritability coefficient of 1.0. Likewise, a population of clones would yield a heritability estimate of 0 (Tesser, 1993). The heritability of a given phenotype is therefore dependent on the context, and cannot be determined once and for all. The heritability coefficient also makes no sense on the individual level, as this is a statistic used to explain variability in a phenotype on a population level.

When reading behavioral genetic research one may come across two types of heritability estimates; namely narrow-sense and broad-sense heritability (Plomin et al., 2001). The former, often referred to as h^2 or a^2, is the most commonly reported in twin studies and is based on only the additive genetic variance. Broad-sense heritability also includes dominance effects and epistasis. Calculating the crude narrow-sense heritability based on MZ and DZ twin pair correlations could be done with Falconer's formula (Falconer & Mackay, 1996):

$$h^2 = 2(r_{MZ} - r_{DZ})$$

where r is the correlation coefficient. The rest of the variance proportion that contributes to similarity between twins in a pair is the shared environment, notated as c^2. This can be found with the following expression:

$$c^2 = r_{MZ} - h^2$$

As the variance components together explain 100% of the variance in a phenotype, they will sum up to 1, and thus the unique environmental variance component will explain the rest of the variance, and can be found with the following expression:

$$e^2 = 1 - r_{MZ}$$

This equation also pertains to the assumption that any variance that is not shared between MZ twins must be due to non-shared environmental influences (Plomin et al., 2001).

One common misconception about the heritability coefficient concerns its accuracy. The heritability estimate is dependent on how a phenotype is measured. If a measurement contains a large degree of measurement error, this would be allocated to the non-shared environmental variance component. As the variance components together explain all the variance of a phenotype, a larger e^2 would necessarily diminish the h^2. It should also be kept in mind that the calculation of heritability is based on several assumptions (as discussed under 5.1.4) which, if not valid, could bias the estimate. Despite these limitations, the heritability coefficient is useful for quantifying the relative importance of genetic influences on a phenotype.

1.1.3 Twin model fitting

Estimation of variance components from twin data can be done with a multitude of methods, including multiple regression analysis (Defries & Fulker, 1985). However, the most common statistical technique for this purpose is structural equation modeling (SEM). SEM is a statistical technique that can be applied for testing hypotheses about the causal influences of measured variables, and is more flexible and comprehensive than regression analyses (Bollen, 1989). The process usually starts out with a hypothesis specified as model, after which alternative models are tested until a satisfactory fit to the observations is obtained. SEM models can be expressed graphically in path diagrams. Many advanced SEM approaches have been used to estimate variance components from twin data, such as multilevel modeling (Guo & Wang, 2002), genetic mixed linear modeling (Ha et al., 2007) and discrete time frailty modeling (Harkonmäki et al., 2008), but the present thesis focus on more basic SEM strategies.

Using SEM on twin data is done by utilizing the variance and covariance within and between MZ and DZ twin pairs on one or several phenotypes. For a univariate ACE twin model, the variance-covariance matrices for MZ (on the left) and DZ (on the right) twins would look like this (Plomin et al., 2001):

$$\begin{bmatrix} A+C+E & \\ A+C & A+C+E \end{bmatrix} \qquad \begin{bmatrix} A+C+E & \\ \frac{A}{2}+C & A+C+E \end{bmatrix}$$

The variance is represented by the diagonal elements and the covariance by the off-diagonal elements. The only difference between the MZ twins and DZ twins in the model is that DZ twins share half of the additive genetic variance, whereas MZ twins share all.

In Figure 1, the ACE model is also depicted as a path diagram. The expected variance-covariance matrices are based on the values we hypothesize for the variance components a^2, c^2 and e^2. For this approach to be feasible it is necessary to use some form of SEM software, such as Mx (M. C. Neale et al., 2003) or OpenMx (Boker et al., 2011) which are designed specifically for handling twin data. The procedure used with software such as these starts out by specify the model in a script, and provide starting values (which often are more or less informed guesses) for the a, c and e parameters. With the use of optimization tools, the software uses an iterative process to test different values for the parameters from the starting values, until an optimal solution is found that reproduces the observed variance-covariance matrix as closely as possible.

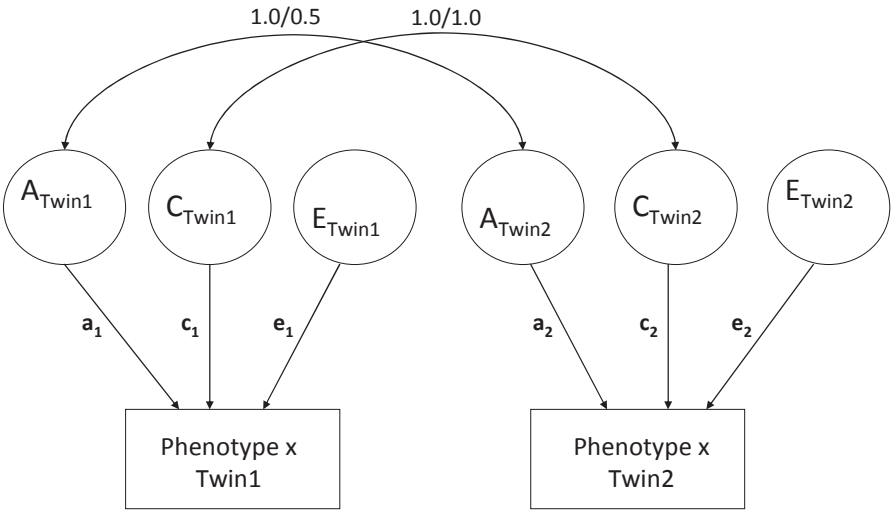


Figure 1. *The classical univariate ACE model formalized as a path diagram. The variance of the latent variables A, C and E are fixed to 1.0, and the path coefficients a, c and e are estimated based on the variance and covariance for the MZ and DZ twins on the measured phenotype. The A factors correlate 1.0 for MZ twins and 0.5 for DZ twins. The parameter estimates are set to be equal for twin1 and twin2. Thus for simplicity, the path diagrams of twin models are often drawn for just one of the twins.*

To be able to estimate the parameters, the model has to be identified. The ACE model is an example of an identified model, which means that it has at least as many supplied statistics from the data as it has parameters to be estimated (M. C. Neale & Maes, 2000). An identified model has the characteristic that the best fit to the data (i.e. the smallest distance between the observed and expected covariance matrix) is achieved with one and only one set of parameter values (Plomin et al., 2001). Twin model fitting is generally conducted by first fitting the full model, which is often an ACE model. The full model can also include sex differences on the parameters (explained under 3.6.3). By dropping parameters from this model, we can test to what extent the resulting set of parameter estimates can still account for the observed covariance. For instance, one can drop the C parameter, and thus assume that shared environmental effects are not important to explain variance in the given phenotype. The procedure of dropping parameters from the full models is often referred to as model trimming. The resulting nested submodels (i.e. AE, CE and E models) are directly comparable to the full model. With fewer parameters, the model will obtain a poorer overall fit than the full model. However, as a rule of thumb, simpler models are preferred over the more highly parameterized, as long as they do not fit significantly worse. In order to choose between nested submodels that do not have significantly poorer fit than the full model, fit indices can be applied (as explained under 3.6.5).

The model fitting procedure described above can be extended to include multiple phenotypes by utilizing the cross-twin cross-trait statistics. The multivariate approach is feasible for answering more complex questions than just how heritable a phenotype is, such as why phenotypes covary, and to what extent genetic and environmental contributions can account for stability and change in phenotypes measured over multiple time-points.

More details of optimization, fit indices, sex differences and the specific modeling techniques applied in the present thesis are described under the methods section.

1.1.4 Life events and social constructs as phenotypes in twin studies

According to the first law of behavior genetics (Turkheimer, 2000), all human behavior traits are heritable, and indeed this has been found for a wide range of phenotypes (Bouchard & McGue, 2003). As this has been more or less accepted as a fact, behavioral genetic research has also moved on to study phenotypes that are less “behavioral”. Examples of these are divorce and other stressful life events, political attitudes and medical benefits, which are harder to imagine could be heritable in the sense that they are coded for by specific genes. These phenotypes have traditionally been studied within the social sciences, where biology has been more or less ignored

as a contributing factor (Fowler et al., 2008). However, in order to explain as much variance as possible in phenotypes, biology should also be taken into account.

Already in the early 1990s, twin studies were conducted on various types of stressful life events to investigate genetic and environmental contributions (Kendler et al., 1993; McGue & Lykken, 1992; Plomin et al., 1990). The studies by Kendler et al. and Plomin et al. divided stressful life events into which were controllable or personal (i.e. influenced by the individuals themselves) and those that were uncontrollable or due to more extrinsic influences. The heritability of the controllable events varied between 14 and 53%, whereas the heritability of uncontrollable events varied between 0 and 18%. More recent studies include political voting behavior (Fowler et al., 2008), sick leave (Svedberg et al., 2012) and disability pension (Harkonmäki et al., 2008; Narusyte et al., 2011). It is reasonable to ask why such phenotypes are heritable. The studies on stressful life events have suggested that the heritability of these phenotypes to some extent can be explained by genetic influences on personality characteristics (Kendler et al., 1993; McGue & Lykken, 1992), and, in the study on voting behavior, through genetic variation in prosocial behavior (Fowler et al., 2008). Thus, one can imply that genes do not necessarily influence life events in a direct manner, but rather through people's behavior as regulated by personality. Naturally, it has also been suggested that the heritability of disability pension to a large extent may be explained by the heritability of mental and somatic disorders (Harkonmäki et al., 2008; Narusyte et al., 2011) and other heritable health indicators, such as birth weight, chronic childhood disease and deviant behavior (Narusyte et al., 2011). For sick leave, the heritability could to a large extent be explained genetic factors for diseases and functional ability (Svedberg et al., 2012).

1.2 Personality and personality disorders

All human beings have a fairly persistent pattern of behavior and reactions that characterize them and make them unique. One of the earliest theories about personality can be traced back to Hippocrates and Galen and the doctrine of the four humors (Maher & Maher, 1994). Here it was posited that bodily fluids combined with humors to create four different temperamental styles; sanguine, phlegmatic, choleric and melancholic. Imbalance in the humors was assumed to be the cause of pathology (Maher & Maher, 1994). Since then, various theories about personality and psychopathology have developed, for instance those of Kraepelin, Bleuler, Freud, Schneider, Kretschmer (Oldham, 2005) and Eysenck (Eysenck, 1947).

Personality in adulthood is assumed to be based on childhood temperamental characteristics (Caspi, 2000; Rothbart et al., 2000). Normal personality refers to an individual's

enduring patterns of cognition, emotions, motivation and behavior that is activated in different situations (Heim & Westen, 2005). There exist several models of normal personality, such as the five-factor model, which emphasize five broad, and fairly universal domains; neuroticism, extraversion, openness to experience, agreeableness and conscientiousness (R. R. McCrae & Costa, 1997). For some individuals, the patterns constituting normal personality may become dysfunctional and rigid. In these cases the concept of personality disorders (PDs) becomes relevant. Many argue that PDs are simply maladaptive extremities of normal personality traits (Cloninger, 2000; Livesley et al., 1998; R. R. McCrae et al., 2005; Widiger & Costa, 1994), although there is less agreement on the exact nature of this correspondence (Markon et al., 2002).

1.2.1 Classifying and diagnosing PDs

The dominating nomenclatures for classification of mental disorders are the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders (DSM) (APA, 2000) and the World Health Organization's International Classification of Diseases (ICD) (WHO, 1992), which are largely overlapping. In May 2013 the fifth edition of the DSM was published, but the focus in this thesis will be on the DSM-IV, as we have used DSM-IV PD criteria.

In DSM-I (1952) and DSM-II (1968), PDs were defined by short, non-theoretical descriptions that clinicians could match their patients against, regardless of the patients' functional impairment (South & DeYoung, 2013). With DSM-III (1980), specific criteria that could be observed and measured were introduced for each PD, making it less arbitrary which patients received a diagnosis (Oldham, 2005). A multiaxial system was also introduced, were the more episodic mental disorders were placed on Axis I, whereas PDs which were assumed to be more persistent, were placed on the Axis II to ensure that they were not ignored by the Axis I disorders (Oldham, 2005). The DSM-IV was the result of a long process of literature review, field trials and data analyses, and was published in 1994 (Oldham, 2005). In this version, PDs are defined as enduring patterns of inner experience and behavior that deviate markedly from the expectations in an individual's culture, are pervasive and inflexible, onset in adolescence or early adulthood, are stable over time, and lead to distress and impairment (APA, 2000). There are 10 PDs in the DSM-IV, organized into three clusters on the Axis II division; cluster A, B and C. Cluster A is characterized by eccentric and odd traits, and comprise schizoid, schizotypal and paranoid PD (APA, 2000). Cluster B is characterized by dramatic, emotional and erratic traits, and comprises narcissistic, borderline, histrionic and antisocial PD (APA, 2000). Cluster C PDs are characterized by anxious and fearful traits, and comprises avoidant, dependent and obsessive-compulsive PD (APA, 2000). In addition, there is a category for personality disorder not otherwise specified for

mixed presentations of fulfilled criteria, as well as two PDs in the appendix; depressive PD and passive-aggressive PD. These will, however, not be discussed in the present thesis. A text revision of the DSM-IV (DSM-IV-TR) was launched in 2000, but with few changes in the PD texts (Oldham, 2005).

Although the DSM-IV was an improvement compared to the earlier versions, it has been subject to criticism. It has been argued that the evidence for keeping PDs on a separate axis is scarce, as Axis II disorders are found to have a similar etiological basis and course as Axis I disorders (Livesley & Jang, 2008). The extensive comorbidity between Axis I and II disorders (Friborg et al., 2013; Grant et al., 2008; Lenzenweger et al., 2007) also represent a strong argument against the distinction. PD diagnoses have been criticized for being too heterogeneous, as individuals may be assigned the same diagnosis based on completely non-overlapping criteria (Cloninger, 2000). In addition, the categorical approach to mental disorders has been heatedly debated, and the thresholds required for a diagnose are generally regarded as arbitrary (South & DeYoung, 2013).

1.2.2 Measuring PDs

Measuring latent constructs such as PDs is challenging, as these cannot be observed directly but must rather be inferred from a pattern of thoughts and behavior that have been present over an extended period of time. To measure PDs, epidemiological and clinical studies typically use various structured or semi-structured diagnostic interviews or self-report questionnaires. Many of these are based on the criteria in the DSM, but instruments stemming from other conceptualizations of PDs also exist.

In a structured interview procedure, the interviewer assesses PDs by asking a predetermined set of questions. In semi-structured approaches, the interviewers may also ask additional questions to clarify which score should be set for each criterion (McDermut & Zimmerman, 2005). Most structured interviews for PDs have adequate reliability and validity (McDermut & Zimmerman, 2005). However, structured interviews also have some limitations, such as low reliability due to few items (Livesley & Jang, 2008), underreport (Moum, 1998), social desirability (Westen, 1997) and rater bias (Zimmermann, 1994).

The self-report methodology for assessing mental disorders started after World War I, when shortage of psychiatrists created a need for an alternative to the traditional psychiatric interview (Derogatis et al., 1974). As interviews are time consuming and expensive to conduct, self-report questionnaires represent a less resource demanding option. A questionnaire is typically comprised of items stated as assertions that respondents rate to what extent they agree with.

Limitations with self-report questionnaires are that they can result in more false positives than interviews (McDermut & Zimmerman, 2005) and that they may have less specificity than interviews (Kendler et al., 2007).

Limitations with PD measures should be taken into account both in clinical and epidemiological studies. The use of a single measure of PDs that include measurement errors could result in over- or underestimations of prevalence, or produce bias when investigating associations (Yanez et al., 1998). In twin studies, measurement imperfection may produce an artificially high estimate of the unique environmental influences (E) on the expense of additive genetic influences (A). The best method to ensure that PDs are captured as precisely and validly as possible may be to combine different methods of assessment or to perform measurements at different time-points. This approach allows modeling of PDs as latent constructs. Genetic and environmental contributions to the latent construct can thus be assessed corrected for measurement errors, as the non-shared variance between the measures or time-points is separated out.

1.2.3 Categorical and dimensional conceptualizations of PDs

The PDs in the DSM-IV are categorical, meaning that a disorder is present only when the patient exceeds a pre-defined threshold. The thresholds vary for each PD, but usually 3 to 5 criteria scored as "present" are needed for a PD diagnosis. An alternative to the categorical approach is dimensional models that conceptualize PDs as quantitatively rather than qualitative different from normal personality. The dominating view of PDs clearly appear to be on the dimensional side, for which strong empirical evidence already exist (Eaton et al., 2011; Samuel & Widiger, 2004; Trull & Durrett, 2005; Widiger et al., 2009; Widiger & Mullins-Sweatt, 2005). The dimensional approach is also in line with the mode of thought in behavior genetics, where complex phenotypes such as PDs are assumed to be caused by multiple genes for which the effects combine both additively and non-additively (Plomin et al., 2001; Rutter, 2006; South & DeYoung, 2013). As individuals have a varying amount of risk alleles for PDs, this will create a dimension of liability (South & DeYoung, 2013). Despite the eagerness to change categorical PD diagnoses into dimensions, it is not straightforward how this could be implemented. Meanwhile, the more convenient categorical approach is maintained.

The issue of categories versus dimensions is relevant to the present thesis, as the PD variables used were constructed as sum-scores (see section 3.4.1).

1.2.4 Behavioral genetic research on PDs

At the time DSM-III was published, PDs were assumed to be caused by psychosocial adversity, and not by genetic influences (Livesley & Jang, 2008). This assumption has changed as more studies have found evidence for genetic influences on PDs. The first twin study on the whole range of DSM-III PDs found the heritability to range between 0.28 and 0.79 (Torgersen et al., 2000). In a large sample based on the Norwegian Institute of Public Health Twin Panel, it was found moderate genetic influences on DSM-IV PDs, and the heritability varied between 0.21 and 0.41 (Kendler et al., 2008; Kendler et al., 2006; Reichborn-Kjennerud et al., 2007; Torgersen et al., 2008). These estimates could be argued to be surprisingly low, compared to many other mental disorders with heritabilities typically ranging from 0.50 to 0.60 (Kendler et al., 2011). It has been hypothesized that the low heritability could be due to measurement imperfection in the interview measure used (e.g. Reichborn-Kjennerud et al., 2007), as discussed under 1.2.2. This hypothesis was supported in two studies that corrected for measurement errors by using both interview and self-report measures, and found that the heritability estimates for cluster A and B PDs increased to vary between 0.55 and 0.72 (Kendler et al., 2007; Torgersen et al., 2012).

Traits underlying PDs have also been found to be heritable. With the use of the Dimensional Assessment of Personality Problems – Differential Questionnaire (DAPP-DQ), the heritability of the PD trait scales mostly varied between 0.40 and 0.50 (Jang, Livesley, Vernon, et al., 1996). Although PD diagnoses are usually not applied to children (APA, 2000), PD traits based on the DSM-IV criteria were assessed in a sample of 112 twins pairs aged 4 to 15 years, and the heritability was found to vary between 0.50 to 0.81, depending on PD diagnosis (Coolidge et al., 2001). Normal personality dimensions and traits are also heritable, with estimates quite close to those found for PDs (0.40-0.60) (Bouchard & Loehlin, 2001; Jang, Livesley, & Vernon, 1996).

1.2.5 Consequences of PDs

In the DSM-IV definition of PDs it is stated that the PD symptoms must cause impairment for the individual in social, occupational or other important areas of functioning (APA, 2000). PDs are found to account for more impairment than major depressive disorder (Skodol et al., 2002), and impairment is found to increase as a function of the number of PD criteria fulfilled, regardless of PD type (Nakao et al., 1992). As PDs emerge in adolescence or early adulthood, impaired functioning is particularly severe, as this can contribute to delay in occupational and social development (Grilo & McGlashan, 2005). The impairment in functioning has also been found to persist even after the PD symptoms have improved (Seivewright et al., 2004).

In addition to studies focusing on the global functioning for individuals with PD diagnoses, some studies have investigated more specific areas of functioning. For instance, individuals with PDs are found to be more likely to be separated, divorced or never married (Drake & Vaillant, 1985; Zimmerman & Coryell, 1989), have poorer social functioning (Drake & Vaillant, 1985; Torgersen, 1984), more symptomatic suffering and concerns about health (Noren et al., 2007), more problems maintaining job positions (Noren et al., 2007), and more often receive disability benefits (Knudsen, Skogen, et al., 2012; Korkeila et al., 2011; Modestin & Villiger, 1989; Østby et al., submitted) than those without PDs. Individuals with PDs have also been found to be granted disability pension at a younger age than individuals with anxiety or depression (Korkeila et al., 2011). It should be noted that some of the above mentioned studies are old and have very low sample sizes. More studies are therefore needed on consequences of PDs.

1.3 Medical benefits

Various types of medical benefits are provided by most welfare countries, and serve as economical safety nets for those who have reduced work capacity due to illness, disease or injury. The Norwegian National Insurance scheme represents the cornerstone of the Norwegian pension and social security scheme and was introduced as a statute on January 1st 1967 (NOU, Norwegian Official Reports 2000:27) and updated in 1997 ("Folketrygdloven [National Insurance Act]," 1997). Membership is as a general rule compulsory for those residing or employed in Norway (Regjeringen, 2013). The scheme is financed by the employers, government subsidies and income taxes. The main types of benefits are sick leave benefits, medical- and vocational rehabilitation benefits (later replaced by work assessment allowance) and disability benefits. In most of the countries that provide medical benefits for their inhabitants, information on granted benefits are recorded in large official registries or company databases.

In 2013, the sick leave rate for the whole population (defined as proportion of work days lost over the proportion of appointed work days) was approximately 6% in Norway (SSB, 2013a). The proportion of individuals aged 18 to 67 that received disability pension in 2013 was 9.3% (NAV, 2013).

1.3.1 Sick leave benefits

Sick leave benefits are provided as financial aid for members of the National Insurance Scheme that are unable to work due to illness, disease or injury. In order to be eligible for sick leave benefits, an individual must have been in occupational activity (including attempts to obtain work for those who are unemployed) for four weeks prior to sick leave. Working individuals are usually

entitled to 3 days of self-certified sick leave for up to four times within 12 months, but for longer durations a medical certification provided by a physician is required. The first 16 days of sick leave is paid by the employers, and thereafter mandatorily covered by the National Insurance Scheme as daily cash benefits for a duration up to 260 working days (52 weeks) (NOU, Norwegian Official Reports 2010:13). When an individual has received daily cash benefits for 260 days the last three years, a work period of 26 weeks is required to regain the right to this benefit ("Folketrygdloven [National Insurance Act]," 1997). Work related interventions within the work place should be implemented for individuals that have been on sick leave for eight weeks ("Folketrygdloven [National Insurance Act]," 1997). If these interventions cannot be implemented, or if they do not lead to regained work capacity, it is required that medical or vocational rehabilitation is implemented as soon as possible. The option of graded sick leave benefits (20-100%) can be provided for individuals that are still able to work despite reduced capacity. The daily cash benefits is set to 100% of the individual's pensionable income, whilst for self-employed individuals, the sick leave benefits is set to 65% of the income and is paid after 17 days of sick leave, and then covered for 248 days (Regjeringen, 2013).

1.3.2 Medical and vocational rehabilitation

One of the challenges for individuals on long-term sick leave is to be able to return to work. Many OECD countries have a "rehabilitation-before-benefit" principle, to avoid that individuals that could restore working capacity transit to disability pension benefits (OECD, 2010b). In Norway, there have been two types of benefits with this aim, namely medical and vocational rehabilitation. The difference between these and sickness and disability benefits is that they require active efforts from the receivers.

Medical rehabilitation benefit can be provided for individuals that are still incapable of returning to work after the sick leave allowance period has expired. The intention of the benefit is to provide financial aid while individuals undergo medical treatment or work related interventions aimed at restoring work capacity. Prerequisites for this benefit are the individual must have been a member of the National Insurance Scheme for at least three years, be between the age 18 to 67, and have a disease or injury that reduces work capacity by at least 50% ("Folketrygdloven [National Insurance Act]," 1997). The rehabilitation benefit is usually given for 52 weeks, but can in some cases be extended with additional 52 weeks ("Folketrygdloven [National Insurance Act]," 1997).

Vocational rehabilitation benefit is given to individuals that are occupationally handicapped due to disease or injury and for which the work capacity is reduced by at least 50%.

The benefit is given to ensure income for individuals between the age 19 to 67 that undergo rehabilitation aimed at restoring work capacity and for compensating for the expenses that follows the rehabilitation interventions ("Folketrygdloven [National Insurance Act]," 1997). An individual can also receive sick leave benefits when on vocational rehabilitation (NOU, Norwegian Official Reports 2000:27).

The work assessment allowance was introduced on March 1st 2010 to replace the previous arrangements time-limited disability pension, medical rehabilitation and vocational rehabilitation (NOU, Norwegian Official Reports 2010:13).

1.3.3 Disability pension

Many OECD countries provide different types of disability benefits for their inhabitants (OECD, 2010b). Disability pension (DP) is a more permanent medical benefit than sick leave and rehabilitation benefits and are granted to individuals with poor prospects of improved working capacity in the future. In Norway, individuals aged 18 to 67 years whose work capacity is reduced with 50% or more as a cause of illness, disease, injury or other disability due to a medical condition, are entitled to DP after relevant treatment and rehabilitation (NOU, Norwegian Official Reports 2000:27). To be eligible for DP, one must have been a member of the National Insurance Scheme for three years prior to becoming disabled. A DP consists of a basic pension in addition to a supplementary pension and/or special supplement (Regjeringen, 2013). Individuals that are born disabled, for instance due to pervasive developmental disorders, mental retardation, learning disorders, or severe injury in childhood, or have become disabled before age 26 are also eligible for DP. For individuals that have been working, a sick leave period of one year succeeded by medical and/or vocational rehabilitation is most common before DP is granted.

A DP can be graded (20-100%) or granted full-time. In Norway, there was also the possibility for individuals for whom there was uncertainty with regard to future work capacity to be granted a time-limited DP between January 1st 2004 and March 1st 2010.

1.3.4 Increasing rates of sick leave and disability pension benefits

Sick leave rates are high in countries such as Norway, Finland, Sweden and the Nederlands (OECD, 2010b). The past two decades, there has also been reported increasing trends for medical benefits in OECD countries (NOU, Norwegian Official Reports 2007:4; OECD, 2010b; Ose, 2010), and particularly in younger populations (Besseling et al., 2008). This is considered problematic, as sick leave and DP benefits generate massive public finance costs to society. In 2000 and 2007, the spending on DPs alone in OECD countries constituted on average 1.2% of the

gross domestic product (GDP), and about 2% of the GDP when sick leave benefits were included (OECD, 2010b). In Norway, the expenditure on medical benefits was much higher; 5.1% of the GDP in 2000 and 4.8% in 2007 (OECD, 2010b). The costs are greater for individuals with early onset of DP, as these will need benefits for a longer duration than those granted DP later in life.

1.3.5 Research on sick leave

Research on sick leave is challenging, as this is a complex phenomenon with many potential risk factors (Dekkers-Sanchez et al., 2008) and with varying definitions and processes of certification across countries (Henderson et al., 2011). The majority of studies on sick leave originate from the northern part of the Western world, including Finland, Norway, Sweden, the Nederlands, the UK and the USA. A limitation within field of sick leave research is the lack of an international standard for how to define sick leave (Hensing, 2004). Varying definitions and certification processes make it difficult to compare studies. There is also great variability in how short-term sick leave is separated from long-term sick leave (Henderson et al., 2011). Definitions of long-term sick leave mostly vary from sick leave >7 days to sick leave >6 months. In the studies conducted for the present thesis, we have defined long-term sick leave as sick leave >16 days. To narrow down the scope, the focus will primarily be on studies that have used some form of long-term sick leave measure, as this is also most relevant to this thesis. Long-term sick leave will be referred to as LTSL in the remaining part.

1.3.6 Risk factors for LTSL and DP

Health-related factors

In Norway, musculoskeletal- and mental disorders are the most common causes for LTSL and DP (Knudsen, Overland, et al., 2012; Ose, 2010). In addition to specific disorders and diagnoses (Hemingway et al., 1999; Jansson et al., 2013; Kivimaki et al., 2007; Pietikainen et al., 2011; Ropponen et al., 2011), several health-related factors are found to be risk factors for LTSL and DP. For LTSL, pain (Andersen et al., 2012; Eshoj et al., 2001; Heijbel et al., 2006), smoking (Skillgate et al., 2009), and obesity (Vingard et al., 2005) have been found to influence the risk. For DP, poor self-perceived health (Krokstad et al., 2002), pain (Overland et al., 2012; Pietikainen et al., 2011; Ropponen et al., 2013), smoking (Harkonmaki et al., 2007; Pietikainen et al., 2011), heavy alcohol consumption (Harkonmaki et al., 2007), obesity (Harkonmaki et al., 2007; Ropponen et al., 2011), frequent use of analgesics (Pietikainen et al., 2011), and low birth weight (Gravseth et al., 2007) have been found to be risk factors.

An important point, though, is that the increase in sick leave rates and DP does not appear to be followed by a corresponding increase in the prevalence of typical disorders for medical benefits (Ihlebaek et al., 2007; Ose, 2010). This observation is supported by standard health indicators in OECD countries which show that the public health has improved rather than deteriorated the recent decades (OECD, 2010a). The pattern of improving health could indicate that factors apart from illness and disease can influence liability to LTSL and DP. Some of these factors are summarized below.

Social and environmental factors

There exist a vast number of studies that have investigated various social and environmental risk factors for LTSL and DP. Important risk factors for LTSL have been found to be psycho-social factors (Steenstra et al., 2005), low level of education (Eshoj et al., 2001), unemployment (Eshoj et al., 2001), and work-related factors (Allebeck & Mastekaasa, 2004; Eshoj et al., 2001; Steenstra et al., 2005). A thorough overview of studies on risk factors for short- and long-term sick leave has been presented by Allebeck and Mastekaasa (Allebeck & Mastekaasa, 2004).

For DP, low socioeconomic status (Harkonmaki et al., 2007; Krokstad et al., 2002; Vaez et al., 2007), low level of education (Ahola et al., 2011; Gravseth et al., 2007; Krokstad et al., 2002; Ropponen et al., 2011; Samuelsson et al., 2012), unemployment (Biering-Sorensen et al., 1999), childhood adversities (Harkonmaki et al., 2007), low social support (Albertsen et al., 2007; Sinokki et al., 2010), interpersonal conflict (Appelberg et al., 1996), and various work-related factors (Ahola et al., 2011; Albertsen et al., 2007; Krause et al., 1997; Krokstad et al., 2002) have been found to be important risk factors.

Most of the studies on risk factors for medical benefits do not have adequate design or data for establishing causal relationships, and many have been characterized as having low quality (Allebeck & Mastekaasa, 2004). The risk factors may also vary from country to country as a function of different labor market condition, insurance systems and social conditions (Eshoj et al., 2001). In addition, sex differences have been found on some of these factors, indicating that males and females vary in respect to which factors influence the risk for medical benefits.

It should be noted that phenotypes that are regarded as social or environmental can also be heritable. Examples are education (Branigan et al., 2013) and work-related phenotypes such as work values (Keller et al., 1992) and occupational preferences (Maczulskij, 2013; Tambs et al., 1989).

In Norway it has been speculated in the media that social transmission, for instance through attitudes in the family or community, may be an explanation for the occurrence of

medical benefits and particularly DP. Though the debate recurs occasionally, the empirical evidence for social transmission is scarce. One study investigated to what extent there was an effect of having peers on DP on the sample's propensity to be granted DP (Rege et al., 2012). A one percentage point increase in the DP rate of previously employed neighbors increased the subsequent four-year DP entry rate of employed workers with less than a half percentage point. Another study found that growing up with parents on DP significantly increased the risk for DP in the offspring, with hazard ratios of approximately 2 for both sexes, and suggested that this could be explained by the impact the parents had as role models (Kristensen et al., 2004). Despite the low number of studies on the phenomenon, the discussion is interesting, and to some extent relates to the potential social and medical benefits have to be misused by individuals not entitled to them.

Genetic contributions to LTSL and DP

Most previous studies on risk factors for LTSL and DP have focused on environmental factors such as psycho-social and work-related factors. However, biologic factors such as sex, age and genes can also affect the risk for LTSL and DP. Being female (Albertsen et al., 2007; Gravseth et al., 2007; Haukenes et al., 2012; Steenstra et al., 2005) and having a high age (Heijbel et al., 2006; Steenstra et al., 2005) have been found to be important risk factors for both LTSL and DP. Very limited knowledge exists regarding the extent to which medical benefits are heritable. Only one study has investigated the heritability of LTSL. By utilizing a point prevalence of LTSL (>15 days) in a Swedish twin sample aged 43-65, the heritability was estimated to be 0.36 and no sex differences were found (Svedberg et al., 2012). The heritability of DP was first estimated in a Finnish study, which found that the heritability was 0.36 for DP regardless of diagnosis, whereas DP for specific diagnostic groups was 0.42 for mental disorders, 0.37 for musculoskeletal disorders, 0.48 for cardiovascular disorders and 0.24 for all other diagnoses (Harkonmäki et al., 2008). The study could not test for sex differences due to lack of opposite sexed twins and low prevalence of DP in the sample. A recent Swedish twin study found that the heritability of DP was 0.33 for all diagnoses, 0.49 for mental diagnoses, 0.35 for musculoskeletal diagnoses and 0.27 for all other diagnoses (Narusyte et al., 2011). The study found evidence of qualitative but not quantitative sex differences, which indicate that the pathways to DP may vary for males and females.

1.3.7 The association between LTSL and DP

Most individuals that have been on LTSL are later able to return to work. However, some will transit to DP. It has been calculated from Norwegian data from 1993 to 2000 that the likelihood for being transferred to DP after one year on sick leave was 40% (OECD, 2006). For individuals on medical and vocational rehabilitation, the likelihood was 34% and 22%, respectively (OECD, 2006). For patients under 40 years who were on LTSL for the first time, 9% were granted DP five years later, and the risk for transiting to DP was particularly high for LTSL due to mental disorders (11% of women and 24% of men) (Gjesdal et al., 2005). A phenotypic association between LTSL and DP (Ahola et al., 2011; Hultin et al., 2012) is however, not at all surprising as LTSL usually is a prerequisite for DP. A more important question would be why some individuals transit to DP, whereas others return to work. Could this transition be due to shared risk factors between LTSL and DP? And if this is so – which risk factors are involved? To reach a better understanding of the association between LTSL and DP it is necessary with studies that can investigate common and specific genetic and environmental contributions.

1.3.8 Associations between mental disorders and medical benefits

LTSL du to mental disorders has increased in Western countries the last two decades (Hensing et al., 2006), and more and more inflows to DP are also due to mental disorders (OECD, 2006). In Norway, incidence of DP granted for mental disorders was found to be more than doubled in the age group 16 to 29 between 1988 and 2000 (Andersson et al., 2006). As mental disorders most often emerge in adolescence and early adulthood (Kessler et al., 2005) they may be detrimental to education and subsequent employment (Suvisaari et al., 2009).

Several studies have found that common mental disorders such as anxiety and depression are important risk factors for sick leave (Henderson et al., 2011; Knudsen et al., 2013; Shiels et al., 2004; Stansfeld et al., 1995), and that recurrence rates for sick leave due to mental disorders are high (Koopmans et al., 2010). Mental disorders are also important for DP, as it has been found that DP due to any diagnosis can be predicted by severity of depression (Bultmann et al., 2008), common mental disorders (Ahola et al., 2011; Mykletun et al., 2006) comorbidity between mental disorders (Ahola et al., 2011) and psychological distress (Rai et al., 2012). However, few studies have investigated effects of less common mental disorders on medical benefits.

1.4 Areas in need of more studies

There are relatively few studies on genetic and environmental contributions to PDs. Despite this, the evidence that PDs to some extent are heritable is strong. The variability in heritability

estimates, however, indicates that there is a need for more studies, preferably with large sample sizes and designs that render it possible to remove the influence of measurement errors. In particular, knowledge on the heritability of Cluster C PDs corrected for measurement error has been lacking. In the first paper in this thesis we therefore aim to investigate the heritability of DSM-IV cluster C avoidant and dependent PD.

Very few twin studies had been conducted on LTSL and DP, and even fewer on young adults. The genetic and environmental associations between LTSL and DP have also been unexplored. The few studies that exist need to be replicated in other samples as there is a great variability in definitions and processes of certification across countries. There is also a need to investigate to what extent there are sex differences on genetic and environmental factors. As it has been found higher prevalence for females than for males for both LTSL (Alexanderson et al., 2005) and DP (Albertsen et al., 2007; Alexanderson et al., 2005; Gravseth et al., 2007; Haukenes et al., 2012) it is reasonable to expect sex effects. Although the assumed phenomenon of social transmission is embraced by the media, the evidence for this is scarce. In Paper 2, we investigate common and specific genetic and environmental contributions to LTSL and DP, and also test for sex effects and sibling interaction.

As mentioned under 1.3.8 there has been an increased focus on the association between mental disorders and medical benefits, but studies on the consequences of PDs for LTSL in particular have been lacking. As PDs are associated with impaired functioning on several life domains and also with increased risk for DP, it is reasonable to assume that they can also increase risk for LTSL. Studies on extreme scores on normal personality traits add support to this assumption, as these have been found to be associated with both short and long-term sick leave (Stormer & Fahr, 2013; Vlasveld et al., 2012) as well as impaired work functioning (Michon et al., 2008). In Paper 3, we aim to investigate the phenotypic association between 10 DSM-IV PDs and LTSL. To find out if any PDs are uniquely associated with LTSL, we also adjust for other PDs. Further, we investigate to what extent genetic contributions to PDs associated with LTSL can account for the heritability of LTSL. Finally, we explore the hypothesis of a causal pathway between PDs and LTSL.

2. RESEARCH OBJECTIVES

The objective for this thesis is to investigate genetic and environmental contributions to PD, LTSL and DP. The main aim is to investigate consequences of PDs on work participation measured as LTSL. The specific aims for each paper are summarized below:

Paper 1

To estimate the genetic and environmental contributions to the latent liability of the DSM-IV cluster C avoidant and dependent personality disorders corrected for measurement error by using two different methods of assessment conducted at different time points.

Paper 2

To investigate the common and specific genetic and environmental contributions to the liability to long-term sick leave and disability pension in young adult Norwegian twins by using biometric twin modeling.

Paper 3

To investigate whether there is an association between DSM-IV personality disorders and long-term sick leave; to identify which of the 10 DSM-IV personality disorders are significantly associated with long-term sick leave and which of these are most important for the association; to investigate to what extent the heritability of long-term sick leave can be accounted for by genetic contributions to personality disorders, and; to explore whether the association between long-term sick leave and personality disorders is causal or due to other factors.

3. MATERIALS AND METHODS

3.1. The Norwegian Institute of Public Health Twin Panel

The Norwegian Institute of Public Health (NIPH) in Oslo has, since 1992, had an ongoing program of twin research, based on the Norwegian Institute of Public Health Twin Panel (NIPHTP) (Harris et al., 2006). The panel contains information on twins that were identified through the Medical Birth Registry (MBR) of Norway. The MBR was established on January 1st, 1967, and receives mandatory notification of all live- and stillbirths of at least 16 weeks of gestation. 15,374 like- and unlike-sexed twins were born in Norway between 1967 and 1979. The twins from the intact pairs born between 1967 and 1974 that were at least 18 years old were invited to participate in a mail-out questionnaire study (Q1) in 1992. The same twins were re-contacted for a follow-up questionnaire study (Q2) in 1998, along with a younger cohort born between 1975 and 1979 (Tambs et al., 2009). Data from Q1 were not used in the present thesis. The Q2 questionnaire, an extended version of the Q1 questionnaire, was sent to 12,700 twins, of which 8,045 (63%) responded after one reminder. These respondents consisted of 3,334 complete pairs and 1,377 singletons. Age in this sample spanned from 18 to 31 years (mean 25.6).

An interview study of mental health was also conducted between June 1999 and May 2004 where approximately 90% of the twins were interviewed within the end of 2002. The interviews assessed lifetime history of psychiatric disorders and substance abuse (Axis I) and personality disorders (Axis II) as diagnosed by the DSM-IV. Participants were recruited from 3,153 complete twin pairs from the Q2 study who had given consent to be contacted again later, and 68 twin pairs drawn directly from the NIPHTP. For this thesis we have used data from the Axis II interview. 2,794 twins (43.3% of those eligible) were interviewed for Axis II disorders. During the interview, age in this sample spanned from 19-36 years (mean 28.1). The majority of the interviews were conducted face-to-face, but for practical reasons, 231 twins (8.3%) were interviewed over the phone. The interviews were mainly conducted by psychology graduate students late in their training and experienced psychiatric nurses who received a standardized training program by one psychiatrist and two psychologists, as well as teachers certified by the WHO. The interviewers received supervision during the data collection. Members of a pair were assessed by different interviewers that were blind to the information obtained from the co-twin.

No information on zygosity is available in MBR. Zygosity was therefore initially determined using questionnaire items previously shown to classify correctly more than 97% of the twin pairs (Harris et al., 2002; Magnus et al., 1983), followed by DNA analyses on a subgroup of the sample. The correct classification of the Q2 twins was 98.0% and 99.1% for the twins that

participated in the interview (Tambs et al., 2009). Misclassification rates of these sizes are unlikely to bias results of twin models (M. C. Neale, 2003).

3.2. The historical-event database (FD-Trygd)

FD-Trygd is a database containing information on the entire population (1992 and onwards) from several sources: Registries at Statistics Norway; the Norwegian Labor and Welfare Organization and the Employment Directorate; and the Norwegian Tax Administration. The database contains information regarding all social security benefits, including e.g., sickness benefits, social assistance, rehabilitation allowance, disability pension and unemployment benefits (Akselsen et al., 2007). The linked dataset also contains detailed information on annual income, employment status (including job seekers) and other demographics (e.g. marital status, number of children and residency (urban/rural)). The register data at Statistics Norway is updated each year, and thus includes annual information on the variables listed above. For the project that this thesis is based on, the data cover the time period from 1998 to 2008.

By using the unique National identification numbers issued to all Norwegians at birth, the data obtained from the twins that participated in the questionnaire and interview studies were in 2011 linked to FD-Trygd, as well as the following registries at Statistics Norway; The Norwegian National Education Database (NUDB) and the Income Register.

After the linkage with the twin data from Q2 and the interviews, the linked dataset now includes detailed, longitudinal information on 7, 710 of the twins. The data collection and linkage have been funded by Norwegian sources.

3.3. Sample

The sample for the first paper consists of the twins that participated in Q2 and the interview study. For the second paper, we used the same sample as in the first paper, but this time it was linked to the registry data from the historical-event database. In the third paper, only the interview data, linked with the historical-event database, was used. The exact sample sizes and number of twins in the different zygosity groups are specified below for each paper. Figure 2 shows an overview of the total sample.

Paper 1

From the Q2 questionnaire study we had data on 8,045 twins (3,334 twin pairs and 1,377 singletons). The complete pairs included 526 monozygotic (MZ) male pairs, 397 dizygotic (DZ)

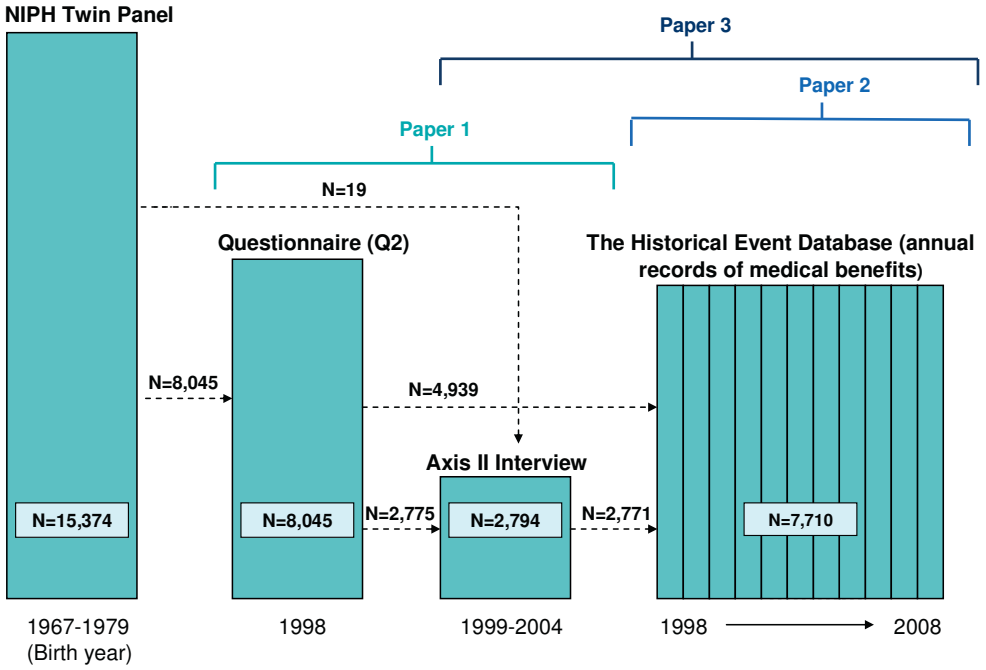


Figure 2. *The samples used in the papers all originated from National Institute of Public Health (NIPH) Twin Panel, which is based on the Medical Birth Registry. More studies not relevant to this thesis have also been conducted, including a previous questionnaire study (Q1) and a recent follow-up of the Axis II interview data.*

male pairs, 777 MZ female pairs, 655 DZ female pairs, and 979 opposite-sex pairs. The single responders included 188 MZ males, 274 DZ males, 159 MZ females, 207 DZ females, and 549 opposite-sex twins.

From the interview study, data from 2,794 responders were valid. Non-participants consisted of 0.8% pairs not willing or able to participate, 16.8% pairs in which only one twin agreed to participate, and 38.9% pairs in which none responded after reminders. In 22 pairs where both twins initially agreed to be interviewed, one of the twins was later unable or unwilling to participate. The sample consisted of 221 MZ male pairs, 116 DZ male pairs, 448 MZ female pairs, 261 DZ female pairs, 340 opposite-sex pairs and 22 single responders.

Paper 2

After linkage, we had valid data on 7,710 twins (3,108 pairs and 1,494 singletons). Of the complete pairs, 492 were MZ males, 354 DZ males, 759 MZ females, 607 DZ females and 896

opposite sex twins. Of the singletons, 210 were MZ males, 286 DZ males, 176 MZ females, 218 DZ females and 592 opposite-sex twins.

Paper 3

The number of individuals with valid interview data after the linkage was 2,771, as 23 declined to participate. For 4 of the 2,771 we lack information on zygosity. The sample for the twin modeling analyses was therefore 2,767 including 1,365 complete pairs, whereof 219 MZ male pairs, 117 DZ male pairs, 436 MZ female pairs, 257 DZ female pairs, 336 DZ opposite-sex pairs and 37 single responders.

3.4 Measures

3.4.1. PDs (Paper 1 and 3)

DSM-IV Axis II PDs were assessed by a Norwegian version of the Structured Interview for DSM-IV Personality (SIDP-IV) (Pfohl & Zimmerman, 1995). SIDP-IV is a comprehensive semi-structured diagnostic interview, and assesses all DSM-IV PDs, including those listed in the DSM-IV appendix. The instrument includes non-pejorative questions organized into topical sections, including subjects such as work style, social relationships and emotions, to produce a natural flow in the interview. The questions address behaviors, cognitions and feelings that have been predominant for most of the past 5 years, and thus are considered to be representative for the individual's long-term personality functioning. This 5 year assumption is supported by empirical evidence of high stability of normal personality traits during adulthood (R.R McCrae & Costa, 1990). Each DSM-IV criterion is scored as 0 = "absent – not present or limited to rare isolated examples", 1 = "subtreshold – some evidence of the trait, but it is not substantially pervasive to consider the criterion present", 2 = "present – criterion is clearly present for most of the last 5 years (i.e. present at least 50% of the time during the last 5 years)" or 3 = "strongly present – criterion is associated with subjective distress or some impairment in social or occupational functioning, or in intimate relationships".

In the analyses of the SIDP-IV data, we used a dimensional approach by constructing the PDs as ordinal variables. The number of criteria scored ≥ 1 was summed, assuming that the liability for each trait is continuous and normally distributed. Due to low prevalence of full PDs, the PD variables were also truncated by collapsing the upper criteria counts into three to five categories to avoid empty cells in the twin analyses. This approach has been used in previous publications on the same sample (Kendler et al., 2006; Reichborn-Kjennerud et al., 2007; Torgersen et al., 2008). These dimensional versions of the PD variables have been tested and

approved with multiple threshold tests that were used to examine whether they can be regarded as differences of severity on a single normally distributed continuum of liability (see e.g. Kendler et al., 2006). Thus, for convenience we refer to PDs, but we are in fact assessing dimensional representations of PDs. The SIDP-IV has previously been used in major Norwegian studies (Helgeland et al., 2005; Torgersen et al., 2001).

In paper 1, PD traits were also assessed by a self-report questionnaire included in Q2; the Dysfunctional Personality Questionnaire (DPQ), which contains 91 items. Some of these items were developed and validated by Svenn Torgersen (Torgersen, 1980) and the rest were selected from three established instruments (Conte et al., 1980; Foulds, 1965; Lazare et al., 1966). The DPQ has been used in previous publications on the NIPHTP sample (Kendler et al., 2007; Torgersen et al., 2012).

3.4.2. LTSL (Paper 2 and 3)

We defined LTSL as sickness absence > 16 days. This was the minimum sick leave period recorded in our dataset. We also included periods of medical and vocational rehabilitation in the LTSL variable, as this reflects a similar condition to LTSL. We separately summed up the total number of sickness absence days, rehabilitation and working days (defined as being registered as employed/working) in the 10 year follow up period; either up to the time of granted DP, death or 2008. The LTSL variable was then defined as a proportion (0-100%) between the cumulative number of sick days and rehabilitation days over the cumulative number of potential working days. The reason for constructing the variable as a proportion was that our sample was young in the period, and thus many would not yet have started working due to education. Had we only summed the number of sick days and rehabilitation days, the amount of sick leave could have been underestimated. The LTSL proportion was further divided into four categories, from 0 to 3 as this variable was positively skewed (skewness: 3.01, kurtosis: 9.95), where "0" = individuals without LTSL in the period (N=2,646), "1" = individuals with up to 5% LTSL in the period (N=2,249), "2" = individuals with 5-15% (N=1,411), and "3" = individuals with >15% (N=1,251). This variable had an acceptable skewness and kurtosis (0.4 and -1.1, respectively) and correlated 0.86 with a sum of the total amount of sick leave days in the period. Only subjects eligible for sickness allowance during the period were included in the analyses; that is - at least one employment period had to be registered.

A total of 153 twins were censored out from the LTSL variable, either due to no work in the period (N=143) or for being granted disability pension before 2000 (N=10).

3.4.3. DP (Paper 2)

The DP variable comprises all twins that were on disability pension in the follow-up period (1998 to 2008). Individuals that had been granted DP before 1998 were also included if they were still on DP in the follow-up period. We constructed an ordinal PD variable scored as 0 = "no DP", 1 = "at least one period of graded (40-90%) DP", and 2 = "only full-time (100%) DP". Those who had died during the follow-up period (N = 34) were scored as missing on this variable.

3.5. Ethics

For the questionnaire and interview data, approval was received from the Regional Ethical Committee and the Norwegian Data Inspectorate, and written informed consent was obtained from the participants after complete description of the study.The linkage of data from NIPHTP with registries at Statistics of Norway was also approved by the Regional Ethical Committee and the participants could decline to participate in the linkage study.

3.6. Statistical analyses

3.6.1 Regression analyses

In paper 1 and 3, ordinal logistic regression analyses using The Predictive Analytics Software Statistics (PASW; originally SPSS) Version 17.0.2 (SPSS, 2009) were performed on the data as all variables were ordinal rather than continuous. In paper 1 backward stepwise ordinal logistic regression was used to select the DPQ items that predicted the number of endorsed criteria in the SIDP-IV. In paper 3 the ordinal logistic regression analyses were first conducted with each PD against LTSL and adjusted for sex. Next, all the significantly related PDs and sex were included in a multivariate analysis.

When the data consists of twins the issue of dependency in the data must be handled. In Paper 1 we solved this by conducting the regression analyses on twin1 in a pair first, and then repeating the analyses on twin2 in each pair. In Paper 3 we conducted regression analyses with generalized estimating equations (GEE) (Dobson, 2002) to correct for statistical dependency in the twin data.

3.6.2 The liability-threshold model

Quantitative genetics was initially developed for continuous and normally distributed traits. However, there are many traits that are defined as categorical entities but are still inherited the same way as quantitative traits (Falconer & Mackay, 1996). An example is mental disorders as defined by the leading classification nomenclatures, where an individual is classified as diseased

if he or she exceeds a predefined threshold. Those below are considered normal. The main principle in the liability-threshold model is that categories (such as having a disorder or not) are hypothesized to be indicators of an unobserved, normally distributed liability that can be estimated as thresholds discriminating between the categories. The principle can be extended to three or more trait categories, provided that the categories can be ordered with respect to increasing liability (Falconer & Mackay, 1996). Most traits are polygenic, meaning that the effects of many risk alleles are needed to express the trait.

The simplest approach to estimating heritability of polygenic and dichotomous measures is to compare concordance rates between MZ and DZ twin pairs. The liability-threshold model can be used to convert concordance rates between twins to tetra- or polychoric correlations (Plomin et al., 2001). The heritability of the trait can thus be estimated by comparing the relative difference in correlations between MZ and DZ twins. However, for comparison of several groups, such as male and female MZ and DZ as well as opposite sexed DZ twins, or for implementation of more complex designs that can answer more questions than just how heritable a trait is, twin model fitting is used. Twin model fitting with binary or ordinal variables, as is done in all papers included in this thesis, is more complex than with continuous traits, and require the mode of thought inherent in the liability-threshold model.

A multiple threshold test can be used to test the assumption that ordered categories reflect differences of severity on a normally distributed liability continuum. This test was conducted in R (R, 2005) and confirmed for the LTSL and DP variables used in this thesis. Previous studies on the same sample as utilized in this thesis have also conducted this test and confirmed that the number of endorsed SIDP-IV criteria for each dimensional PD reflects differences of severity on a normally distributed liability continuum (Kendler et al., 2006).

3.6.3 Twin modeling

The basics of twin modeling were described in section 1.1.3. Below, I describe in more detail the specific models and techniques used in the papers.

Univariate twin model with sex-limitation (Paper 2)

In Paper 2, univariate models were fitted for LTSL and DP separately to estimate heritability and test for qualitative and quantitative sex differences. When sex differences are included in twin models these are often referred to as sex-limitation models, because the strength and type of the genetic and environmental factors controlling expression of the trait may depend on sex (M. C. Neale & Maes, 2000). Quantitative (scalar) sex differences involve the same genetic and

environmental structure, but with different effect sizes for the sexes. Qualitative (non-scalar) sex differences involve different genetic and environmental influences on the trait variance for males and females.

In order to test for qualitative sex differences it is necessary to include a group of opposite sexed twin pairs. In the full model, the genetic correlation between the opposite-sex DZ twin pairs is allowed to vary between 0 and 0.5 (see the A_1A_2 correlation in Figure 1) and the strength of the a, c and e parameter effects are allowed to differ for males and females (i.e. the a_1, c_1 and e_1 parameters in Figure 1 can differ in size from a_2, c_2 and e_2). Testing for qualitative sex differences is done by fixing the genetic correlation between the opposite-sexed DZ twin pairs to 0.5 in a nested submodel. As this test is restricted to opposite-sexed pairs only, it is adequately powered only in large samples. It is also possible to test for qualitative sex differences on the shared environment (C), but this model cannot be compared directly with the genetic qualitative sex-limitation model. We therefore proceeded with a full model that included qualitative sex-limitation on the genetic effects. Testing for quantitative sex effects is done by constraining the a, c and e parameter estimates to be equal across sex in a nested submodel.

We also tested for threshold invariance between twin 1 and twin 2 in a pair within zygosity groups, across same-sexed zygosity groups and lastly the same threshold for all.

Sibling interaction (Paper 2)

Sibling interaction is present if the phenotype of one sibling influences the behaviour in the other (Eaves, 1976). The presence of a sibling interaction can be implied from the difference in phenotypic variance in the trait of interest for MZ and DZ twins. In the presence of a positive sibling interaction effect (cooperation) the variance tends to increase for both MZ and DZ twins, but more for the MZ twins. In the presence of a negative sibling interaction (competition) the variance tends to decrease in both MZ and DZ twins, but more so for the MZ twins (B. M. Neale & Rijsdijk, 2005). The information of variance differences is lost in twin designs that focus on the correlation or covariance structure for MZ and DZ twins (Eaves, 1976) and particularly so for twin models based on ordinal data, where the variance in a trait is usually set to 1.0. Thus, instead of inspecting variances, we included a sibling interaction parameter in the covariance expressions for the different zygosity groups in the univariate models to investigate if there was evidence for twins in a pair affecting each others propensity to LTSL or DP. If a significant sibling interaction is present and not included as a separate parameter, it could be masked as either a shared environment effect (the MZ correlation is less than twice the DZ correlation) if the sibling interaction is positive, or as a dominance effect (the MZ correlation is higher than twice the DZ

correlation) if the sibling interaction is negative. It should be noted that the power to detect a significant sibling interaction effect is generally low in samples of MZ and DZ twins (B. M. Neale & Rijsdijk, 2005) and particularly for ACE models (Rietveld et al., 2003).

Common pathway model (Paper 1)

Common pathway models (also referred to as measurement models) were fitted in Paper 1 to estimate the genetic and environmental influences on the latent PD variables, the specific genetic and environmental influences of the measurements used, as well as the factor loadings or lambdas (indexed as λ_S and λ_I, where $_S$ and $_I$ refer to the DPQ and SIDP-IV, respectively) from the latent PD variables to each instrument measure (Figure 3). When using this modeling technique we assume that each variable (e.g. the PD measures) has variance that is shared and captured by a hypothesized common latent liability to the PD of interest and also variance that is specific (i.e. not shared) to the measures. Covariation between the PD measures is assumed to be caused by the latent PD construct. In the full models we included qualitative and quantitative sex differences. The λ_S and λ_I paths were estimated, but constrained to be equal to make the models identified.

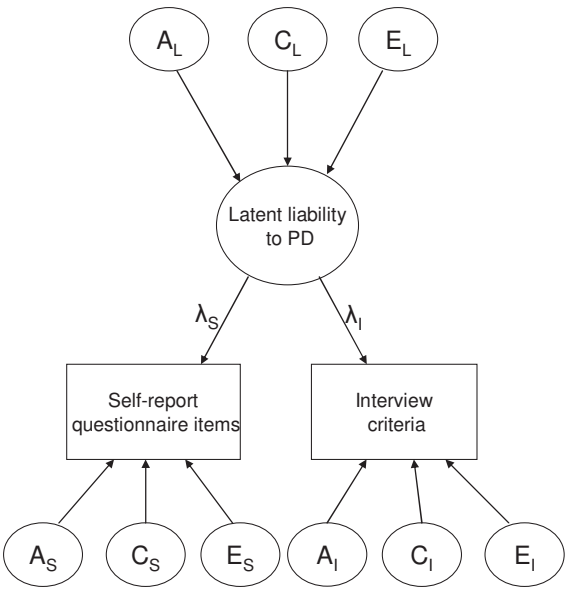


Figure 3. *Common pathway model used in Paper 1, shown for one of the twins in a pair.*

Multivariate Cholesky decomposition model (Paper 2 and 3)

The covariance matrices used in twin models (as discussed under section 1.1.3) have the restriction that they must be positive definite in order to provide sensible estimates. A matrix (M)

is positive definite if it gives a product that is greater than zero when post-multiplied with a vector (z) and pre-multiplied with the same vector transposed (e.g. $z^TMz > 0$). The triangular Cholesky decomposition is a convenient method for constraining maximum likelihood estimates of genetic and environmental covariance matrices to be positive definite. This is done by post-multiplying the lower diagonal matrix with its transpose (e.g. AA^T). The Cholesky method decomposes the variance-covariance structure of the measures into latent factors (A, C and E). The first variable is assumed to be a perfect indicator of the latent factors "A_1", "C_1" and "E_1" that can also explain variance in the second variable. The second variable is also explained by a set of latent factors "A_2", "C_2" and "E_2" not shared between the variables (Figure 4).

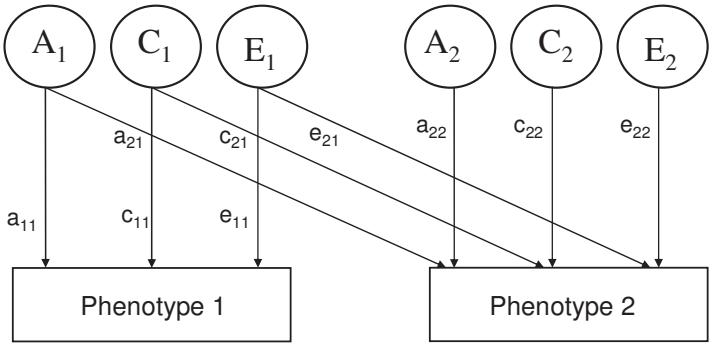


Figure 4. *Bivariate Cholesky twin model, shown for one of the twins in a pair.*

In Paper 2, a bivariate Cholesky model including the variables LTSL and DP was fitted to the data. Due to low prevalence of the DP variable, optimization problems occurred, which were handled by reducing the number of zygosity groups and categories on the LTSL and DP variables. As the MZ- and a DZ twin groups were collapsed without distinguishing same- and opposite-sexed twin pairs, we included sex as a covariate that could moderate the item thresholds to adjust for the differences in prevalence between the sexes.

In paper 3, a four-variate (tetravariate) Cholesky including the variables schizotypal PD, paranoid PD, borderline PD, and LTSL was fitted to the data. Quantitative sex differences were included in the full model, but we could not test for qualitative sex differences as this is problematic in a multivariate Cholesky model (M. C. Neale et al., 2006).

3.6.4 Optimization and fit function

The process of arriving at the best fitting parameter estimates is referred to as optimization. When fitting twin models in software like Mx or OpenMx, standard optimization tools are the maximum-likelihood (ML) and full information maximum likelihood (FIML) functions.

ML expresses the likelihood of a model as a function of the observed data (that is, the variance-covariance matrices, as explained in 1.1.3) and the model parameters. The likelihood is measured as a log-likelihood, abbreviated LL. The overall LL is sought to be maximized by iteratively moving the values of the estimated free parameters to minimize the distance between the observed and expected variance-covariance matrices. The log circumvents the problem of very small numbers that is obtained when a large number of small likelihoods are multiplied. Maximizing the LL is highly computationally demanding, and for multivariate models it can take weeks to arrive at a solution. Specifying good starting values is therefore essential, as this can save time and also reduce the chance of getting trapped in local minima.

In cases where there is missing data in the file, and we want to use all the information available, full information maximum likelihood (FIML) estimation can be used to obtain ML parameter estimates. FIML uses the raw scores for each twin instead of the observed variance-covariance matrices to obtain the highest likelihood of the data. The advantage with using FIML is thus that records with one or more missing values do not need to be discarded. Due to this advantage, twin analyses are now almost exclusively based on raw data with FIML estimation. FIML was applied in all three papers in this thesis. However, FIML is computationally very demanding and also sensitive to starting values, which implies that analyses of a large number of phenotypes may be unfeasible.

The amount of certainty we can have in the resulting parameter estimates can be expressed by likelihood-based confidence intervals (CIs). These can be found by moving away from the obtained parameter estimates in both directions, until the chi-square distributed difference in fit is significant. As the CIs are likelihood-based, they can be asymmetrical around the estimate (Rijsdijk & Sham, 2002).

3.6.5 Goodness of fit

An informed method to choose between alternative models is necessary, as statistical models sometimes have only subtle differences in their overall goodness of fit. The difference in -2LL approaches a chi-square (χ^2) distribution, and can be used as a method to test for significant deterioration in χ^2 in nested submodels. If a nested submodel has a difference in χ^2 that is non-significant, it is typically preferred due to the principle of parsimony. It should be noted, however,

that simulations have shown that p-values obtained for nested submodels in twin studies based on chi-square statistics are often too high (Dominicus et al., 2006). A related and widely used fit statistic that can be used in addition to the χ^2-test is the Akaike Information Criterion (AIC) (Akaike, 1987), calculated as the chi-square minus two times the number of degrees of freedom (χ^2-2df). This calculation favors parsimony by penalizing models that are highly parameterized. The best model is reflected by the lowest AIC value. The AIC can also be used to compare models that are not nested.

4. MAIN FINDINGS

4.1. Paper 1:

Measurement error can deflate estimates of heritability when only one method of assessment is utilized. This problem can be overcome by using different methods of assessment, or by measuring the phenotype on at least two time points. The heritability of avoidant and dependent personality disorder (AVPD and DEPD) has previously been estimated to be moderate. The previous studies did not correct for measurement error, as they were based on a single-occasion measurement. The aim for this paper was therefore to investigate the heritability of dimensional representations of DSM-IV AVPD and DEPD with the use of both an interview and a self-report questionnaire, which were conducted at different time points. AVPD and DEPD were measured with the Dysfunctional Personality Questionnaire (DPQ), of which 8,045 twins responded to, and later 2,794 of the twins were interviewed with the Structured Interview for DSM-IV Personality (SIDP-IV). Ordinal regression analyses were conducted to find the DPQ items that were significantly associated with the interview measures of AVPD and DEPD. Next, measurement models of the PDs were fitted in Mx to estimate genetic and environmental influences on the latent AVPD and DEPD factors. The heritability of the latent factors was estimated to be 0.64 for AVPD and 0.66 for DEPD, which is higher than what has previously been found using single-occasion measurement. 58% of the variance in the DPQ and SIDP-IV could be explained by the latent AVPD factor, whereas the latent DEPD factor explained 48% of the variance in DPQ and SIDP-IV. No evidence of shared environmental effects or sex differences was found for AVPD and DEPD. The SIDP-IV measure had greater specificity in indexing the genetic risk for AVPD and DEPD than did the DPQ measure. Both measures had moderate to strong unique environmental contributions (varying from 31% to 53%), indicating that the amount of measurement error was substantial.

4.2. Paper 2:

In the second paper, we fitted univariate and bivariate twin models in OpenMx to investigate the genetic and environmental contributions to LTSL and DP in a sample of 7,710 twins. The data were extracted from the historical-event database. 65% of the sample had had at least one episode of LTSL (defined as sick leave > 16 days), and 3.3% had DP. The phenotypic correlation between LTSL and DP was 0.86. The strong correlation was expected, as most individuals that are granted DP have first had LTSL. The heritability of LTSL was 0.49, and 0.66 for DP, which indicate that genetic influences are important to explain individual differences in these phenotypes. We found

no evidence for sex differences on the genetic and environmental contributions to LTSL and DP. One hypothesis of the occurrence of LTSL and DP is that this is to some extent caused by social transmission. We therefore tested for significance of sibling interaction and shared environmental effects. The results showed no evidence for shared environmental- or sibling interaction effects, and thus the hypothesis of social transmission was not supported. Instead, the familial transmission of LTSL and DP was due to genetic factors. There was a strong overlap in the genetic and environmental liability for the phenotypes. The genetic correlation between LTSL and DP in the bivariate twin model was 0.82, and the unique environmental correlation was 0.94. Genes common to both phenotypes explained 55% of the phenotypic correlation, whereas the unique environmental contributions shared between the phenotypes accounted for 45% of the phenotypic correlation. In addition to the strong overlap in the genetic and environmental liabilities for the phenotypes, we also found evidence for a genetic factor that was not shared. The specific genetic factor, as well as extreme scores on the common genetic factor could explain why some people progress from LTSL to DP, whereas others return to work.

4.3. Paper 3:

In the third paper, we investigated the phenotypic as well as genetic and environmental associations between dimensional representations of DSM-IV PDs and LTSL. The sample used in this study was 2,771 twins that had been interviewed with the Structured Interview for DSM-IV Personality (SIDP-IV), of which the responses were later linked to the historical-event database. We found that 63.9% of the sample had had at least one episode of LTSL (sick leave > 16 days) in the observation period. The prevalence of any categorical PD diagnosis was 5.1%, and the mean number of subthreshold PD-criteria varied between 0.4 for schizoid PD and 1.9 for obsessive-compulsive PD. The odds ratio (OR) was 2.6 for being in the highest LTSL category compared to the combined lowest categories when fulfilling the categorical DSM-IV criteria for a PD diagnosis. When testing dimensional representations of each of the ten DSM-IV PDs against LTSL and adjusting for sex, we found that all PDs were significantly associated with LTSL ($p<0.05$), except antisocial, narcissistic and schizoid PD. After adjusting for all significantly related PDs and sex, only three PDs remained significantly and uniquely associated with LTSL, namely schizotypal, borderline and paranoid PD. These three PDs were included in a multivariate twin model along with LTSL. The phenotypic correlations between each of the PDs and LTSL were 0.19, 0.17 and 0.13 for schizotypal, paranoid and borderline PD, respectively. Ninety percent of the phenotypic variance in LTSL was not related to the PDs. The remaining 10% was almost entirely due to the influence of shared genetic variance, as the unique environmental variance

shared between the PDs and LTSL was less than 1%. The heritabilities of the phenotypes were 0.26, 0.22, 0.32 and 0.50 for schizotypal PD, paranoid PD, borderline PD and LTSL, respectively. We did not find evidence for shared environmental effects or quantitative sex differences in the twin modeling results. The genetic contributions from the three PDs could account for 20% of the heritability of LTSL. The association between the PDs and LTSL were mainly due to shared genetic factors, which implies that the unique environmental factors that increase risk for PDs are not the same that increase risk for LTSL. The results further suggested that the association between these PDs and LTSL was not causal but instead due to genetic confounding.

5. DISCUSSION

5.1 Methodological considerations

The results in the present thesis should be interpreted in light of some important methodological strengths and limitations. These will be discussed below before I move on to the interpretation of the main findings.

5.1.1 Reliability

Reliability is often defined as the consistency or precision of a measure. Measurement precision is an essential feature in psychological measurement, and can be quantified in various ways to find out to what extent the assessments are free from measurement errors. If variables that have been assessed with poor reliability are included in twin models, the error variance will be captured by the unique environmental factor (E). A large amount of error variance will diminish the influence of the additive genetic (A) and shared environmental (C) factors, and thus the result could be artificially low estimates of A and C. Reliability should be considered for each method of assessment included in a study to ensure that estimates can be evaluated with this potential limitation in mind.

Inter-rater reliability is used to assess agreement between raters. The inter-rater reliability of Axis II disorders are often reported to be in the acceptable area of 0.70, and comparable to Axis I disorders (Grilo & McGlashan, 2005). In the present thesis the SIDP-IV was used to measure PDs. The inter-rater reliability of SIDP-IV has previously been assessed with the use of two raters that scored 70 audio-taped interviews. As none of these respondents obtained a full categorical PD diagnosis, kappas could not be calculated. Instead, intra-class correlations were used to assess the consistency between the raters for the number of endorsed PD criteria at the subtreshold level. These were found to be high; ranging from 0.81 to 0.96. Cronbach's alphas for the sum scores were also high and ranged between 0.72 and 0.89 (Roysamb et al., 2011). In general, inter-rater reliability of dimensional representations of PDs tend to be higher than for categorical PD diagnoses (Grilo & McGlashan, 2005). Test-retest reliability is also a central psychometric property of diagnostic interviews but could not be assessed in this thesis, as the PDs were measured at only one time-point. Structured interviews for PDs generally show good test-retest reliability, although the test-retest is slightly lower than the inter-rater reliability (Bronisch & Mombour, 1998)

The self-report instrument DPQ was also used to assess PDs. This questionnaire was developed by an expert on PDs that were also one of the co-authors of Paper 1. Cronbach's alphas based on polychoric correlations for the AVPD and DEPD items were 0.79 and 0.87, respectively, indicating that internal consistency was good. The correlations obtained between the selected DPQ items and the corresponding SIDP-IV criteria were 0.57 and 0.45, respectively for AVPD and DEPD, indicating that roughly half of the variance inherent in DPQ and SIDP-IV was non-overlapping. It would be desirable if the two measures overlapped more. The issue of poor overlap in diagnostic instruments is also evident for different types of interviews (Oldham et al., 1992) and between interviews and self-report questionnaires (Bronisch & Mombour, 1998). This may not necessarily reflect that the assessment method is inadequate, as the non-consistency could be due to poor construct validity for the PD diagnoses themselves (Livesley, 1998).

5.1.2 Validity

Validity is a broad concept that can have different meanings depending on which setting it is used in. In this thesis, construct validity is the most central type, as this refers to what extent a measure captures the construct it is intended to measure. Thus, when we use the SIDP-IV and the DPQ, we need to know if they are indeed capturing the PD construct. One method to assess the validity of structured interviews is to compare them with consensus diagnoses from clinicians. Findings using this method show that the kappa coefficients for two structured interviews for DSM-III-R Axis II disorders (the Personality Disorder Examination and the Structured Interview for DSM-III-R Personality Disorders) for "any-PD" had an acceptable range of 0.55 to 0.58 in one study (Bronisch & Mombour, 1998) and somewhat lower (0.18-0.37) in another (Pilkonis et al., 1995). Although these results may not be very reassuring, the SIDP-IV is widely used along with other structured interviews for measuring PDs.

A criterion validation of the DPQ has been conducted previously on the NIPHTP sample by using ordinal versions of the DPQ items as predictors and the dimensional SIDP-IV scores as dependent variables in regression analyses. The polychoric correlations between the DPQ scores and the interview scores ranged from 0.39 to 0.61 (Tambs et al., 2009). It is possible that the correlations had been higher if the measurements were conducted at the same time-point.

Another relevant issue is that the PDs used in the present thesis were constructed as dimensional representations instead of categorical diagnoses. In order to validly use these versions of PDs, it is necessary to test that the assumption that dimensional representations of PDs are quantitatively rather than qualitatively different from categorical diagnoses is correct. For this purpose, multiple threshold tests have previously been conducted for all zygosity groups and

found to be non-significant, with p-values > 0.05 (Kendler et al., 2006; Reichborn-Kjennerud et al., 2007; Torgersen et al., 2008). These findings indicate that the number of endorsed PD criteria could be regarded as differences of severity on a normally distributed continuum of liability (Kendler et al., 2006). Based on these findings it is reasonable to assume that the genetic and environmental estimates obtained using the dimensional representations of the PDs will resemble those obtained when using categorical diagnoses.

5.1.3 The use of secondary data sources in research

One of the most important data sources for the present thesis was the data provided by the historical-event database, which is a population-based registry of all types of medical benefits in Norway. These data can be regarded as secondary, as they were not collected specifically for any research project. There are many advantages with registry or secondary data. They are already collected and are thus time and resource-saving, they often include data from a large amount of individuals, and there is a reduced chance for biases like social desirability and misreport as self-report and interview measures can be hampered with. Self-report measures of LTSL and DP, however, are typically found to have good validity, but with somewhat lower sensitivity than specificity (Stapelfeldt et al., 2012; Svedberg et al., 2010). The disadvantages are that the data is not tailored to the specific research purpose and thus may not include all information that the researcher could wish for, the variables may be recorded in a different format than the researcher would have chosen, the data may be of poor quality, it is difficult to test the reliability and validity, and it may require time and resources to convert the data into manageable formats for data analyses.

Reliability issues with secondary data may be the accuracy and completeness of the data (Sorensen et al., 1996). The historical-event database is reliable in regard to which individuals receive medical benefits at specific time-points. The data have been subject to strict routines to avoid errors, and dating and consistency controls have been conducted on most of the data, for instance by comparing them to official statistics (SSB, 2013b). Some errors were still detected by us, such as overlap in the number of sick days and rehabilitation days, resulting in that they jointly add up to more than 365 days a year for some individuals. Some of the individuals were also registered with too few work days, and some had overlap in sick days and work days. This was all managed when we constructed the LTSL variable, but may still have created some bias. There may also be errors that we have not detected. Also relevant to the reliability of the historical-event database is that we could not measure inter-rater reliability for whether a LTSL or a DP is granted or not. It is possible that individuals that should be granted LTSL or DP are not included in the

data, or that individuals that should not be granted LTSL or DP are included. However, I assume that this bias would even out, as some physicians could be more lenient on granting LTSL and DP whereas others could be stricter. The lack of control over the granting process is still a limitation with this study, and should be kept in mind when interpreting the results.

Systematic errors may be a validity issue with secondary data, and pertains to the number of individuals assigned a certain characteristic that truly have this characteristic (Sorensen et al., 1996). In the data used in this thesis, it is possible that some of the individuals received LTSL or DP for non-legal causes, such as by cheating. If this is true for some respondents, the DP and LTSL variables will not measure what they are typically intended to measure, namely work non-attendance due to disease, illness or injuries. To what extent non-valid causes of LTSL or DP is present in our data was not possible to measure. However, it could be argued that this is not a limitation, as we were interested in all types of work non-attendance, regardless of reasons.

5.1.4 Assumptions in quantitative genetics

A common critique of quantitative genetics is that many of the assumptions this method is based on may not always be valid. Assumptions are necessary to conduct twin analyses, as all models are simplifications of the phenomena they are intended to reflect. Although assumptions are necessary, it should be kept in mind that more assumptions would usually mean a higher chance for biased estimates. Below, I will discuss the most common assumptions in twin studies and how they could affect the results in the present thesis if violated.

The assumption of no dominance effects

It is most common to fit twin models that include additive genetic effects (A) and shared environmental effects (C). Thus, we assume that non-additive genetic effects (such as dominance and epistasis) do not contribute to variance in the phenotype of interest, and that the multiple genes involved in creating liability operate additively. This assumption is not strictly necessary, as it is possible to test for dominance effects by including them as a latent factor (D) in the twin model. The drawback of modeling D is that C cannot be included in such a model if we only have MZ and DZ twin data, as this would make the model under-identified.

Before deciding on whether to fit an ACE model or ADE model, one should inspect the phenotypic correlations for the different zygosity groups. If the DZ twin correlations are substantially less than half the MZ correlation, this would indicate dominance effects. In our data, the correlations for males indicated that the liability to borderline PD and schizotypal PD could be influenced by dominance effects. However, borderline PD and schizotypal PD were very rare in

our data, and the CIs for the correlations were wide. High statistical power is needed to detect D effects, and with low-prevalent traits such as these PDs, we would probably not have been able to find evidence for D. If a D effect should be present in our data, however, fitting an ACE model could overestimate the A effects (Coventry & Keller, 2005).

Equal environment assumption

The equal environment assumption (EEA) posits that MZ and DZ twins are similar to an equal extent on exposure for environmental factors required to develop a phenotype (such as a psychiatric disorder). This is evident in the classical twin model, where the correlation between the shared environmental factors is 1.0 for both MZ and DZ twins. It is important to note that MZ being more similar for some environmental exposures is only a problem if this also causes MZ twins to be more similar in their liability to the phenotypes of interest. If MZ twins were found to be dressed more similar than DZ twins by their parents, for instance, this would be of no concern unless this dressing pattern affected MZ twins' proneness to develop PDs, LTSL or DP.

The EEA has previously been tested for several aspects of childhood and adult environmental similarity on twin resemblance for all 10 DSM-IV PDs and found not to be significant (Kendler et al., 2006; Reichborn-Kjennerud et al., 2007; Torgersen et al., 2008). EEA violations have, however not been tested for LTSL or DP, but given that most studies have not found evidence of violation (Rutter, 2006), the chances that it is a problem in this thesis are small. If EEA is violated, the genetic effects could be biased upwards (Rutter, 2006)

Gene-environment correlation and gene-environment interaction

It is assumed that the effects of genes and environment operate in an independent manner. This is an oversimplification, as variation in phenotypes can be affected by correlations and interactions between genes and environment. Correlations between genes and environment (r_{GE}) indicate that there is a non-random distribution of environment across different genotypes (M. C. Neale & Maes, 2000). r_{GE} is traditionally divided into three types; passive, active and evocative (Plomin et al., 1977). Passive r_{GE} arises for instance when a child is provided certain types of environments based on its parents' genotypes. An example of this could be that children of intellectual parents are provided books and other tools that could stimulate academic achievement, or if a child with a parent with a PD experience a negative or confusing rearing style because of the parent's genotype. The child could also seek out certain environments based on his or her genotype, such as books and libraries, which is evident in active r_{GE}. An individual can also evoke certain reactions from the environment based on his or her genotype, such as when children with a

difficult temperament evoke negative reactions from peers or adults. The presence of r_{GE} can be tested in multivariate twin models by investigating whether there is a genetic correlation between a psychological phenotype and an environmental exposure (Plomin et al., 2001). A positive r_{GE} can inflate estimates of A (M. C. Neale & Maes, 2000).

Gene-environment interaction (GxE) involves a genetic susceptibility or robustness to certain environmental exposures. This implies that an individual's reaction to an environmental factor is dependent on his or her genotype. The assumption of no GxE interaction was for long defended by behavior geneticists arguing that this phenomenon was so rare, it need not be taken into account in twin studies (Rutter, 2006). However, many studies the last years have found evidence of GxE on psychological variables, showing that this assumption may be an oversimplification (Caspi et al., 2002; Dunn et al., 2011; Mittal et al., 2008). GxE interaction is perhaps most easy to grasp in diathesis-stress models, where it is assumed that certain types of psychopathology arise as a consequence of the combination of a genetic vulnerability to a disorder and various environmental stress factors. An example of this is the relationship between genetic vulnerability to depression and the effect of stressful life events, where it has been found that the risk for onset of a major depressive episode is a function of both genetic susceptibility and the presence of a stressful life event (Kendler et al., 1995). To test whether a GxE interaction is present it is necessary to include a measure of environment in the twin models, preferably on a very large sample. The consequence of not taking GxE effects into account could be an inflated estimate of E effects (Rijsdijk & Sham, 2002).

Assortative mating

Another assumption in quantitative genetics is random mating, which implies that genotypes in spouses are uncorrelated. The opposite of this is assortative mating, which involves a tendency to choose a spouse genetically similar to oneself. The consequence of higher genetic correlations between spouses is that DZ twin offspring would have a genetic correlation that is higher than what is assumed in the classical twin model (which is 0.5). This effect would be manifested as a spurious C in the twin modeling, and would tend to bias the heritability estimate downwards. The effect is also problematic if for instance spouses correlate on psychopathology but have different mental disorders, as this would make it seem like the mental disorders have a shared genetic liability when that in fact is not the case (Rutter, 2006). It has been found that the effect of assortative mating is high for religious affiliation and education, but moderate to low for phenotypes like personality traits (Hur, 2003; Plomin et al., 2001). If there is bias caused by assortative mating, this is found to affect estimates in twin models to a negligible extent (Maes et

al., 1998). Should assortative mating be a problem in twin models, this would manifest as C effect (Kendler & Prescott, 2006). As we have not detected any significant C effects in this thesis, it is reasonable to assume that assortative mating is unlikely to have biased our estimates.

5.1.5 Miscellaneous methodological and technical issues

Ordinal logistic regression and the assumption of proportional odds

When performing ordinal logistic regression analyses, we assume that the distance between the categories, and thus the odds for being in each category, is the same. This can be tested using the Brant test. If this test is significant, this assumption is invalid. Preliminary tests of proportional odds were performed for Paper 3 and found to be significant. However, when inspecting the odds using multinomial regression, they appeared to be fairly proportional. We therefore proceeded with ordinal logistic regression. This choice could have introduced bias in regard to which PDs were selected, but preliminary analyses showed that the selected PDs were fairly robust regardless of type of regression analyses performed.

Truncation:

In Paper 1 and 3, the PD variables were used as dimensional representations by summing the subthreshold scores ≥1. The resulting PD variables were also truncated by collapsing the upper criteria counts into three to five categories to avoid empty cells in the twin analyses. Preliminary analyses demonstrated that the results from the regression analyses were quite similar whether we used truncated or non-truncated PD variables. To be able to compare ORs for the PD variables in Paper 3, it would have been more feasible to use standardized scores. However, as we were not interested in the ORs per se, but rather which PDs were significantly associated (and p-values are identical for standardized and unstandardized scores), we found it meaningful to use the method of constructing PDs used in previous publications from this research group.

Testing of submodels and parameter dropping in multivariate models:

In all three papers, we have followed the procedure of dropping full sets of parameters (all "c"s, all "a"s etc). When doing this, we risk that some of the paths we drop could have been significant. For instance, it could be that one of the c-paths was significant, but we would be ignorant to this, as we did not try to fit the model by dropping paths one by one. However, by running all possible submodels from a full model, we risk overfitting models by capturing minor fluctuations and random effects. At the same time, it could be questioned why we did not drop more paths. For instance, in Paper 3, some of the paths' lower confidence intervals in the best-fitting Cholesky

model reached zero (paths a42, a43, e41, e42, and e43), meaning that they were not statistically significant.

Statistical power

The twin models fitted in this thesis were mostly based on ordinal measures of PDs, LTSL and DP. DP also had a very low prevalence. Simulations have shown that the power in twin analyses is much lower for ordinal and particularly for binary measures compared to continuous measures. Power also increases with increasing prevalence in a trait (M. C. Neale et al., 1994). The most optimal method would thus be to use continuous variables whenever this is possible, as this would yield more power to detect small effects in the data. As both ordinal and low prevalent phenotypes were included in the analyses, we cannot exclude the possibility that significant sex effects and shared environmental effects could have been revealed with continuous variables and a larger sample size.

Causality

If two variables are correlated, twin models can help guide decisions on whether this could be due to a causal relationship. In Paper 3, a Cholesky model was used to explore whether the association between selected dimensional PD sum scores and LTSL could be a causal one. However, as mentioned in the paper, a Cholesky model cannot be used to reach a definite conclusion on whether a causal association exists or not. For this purpose, a more formal model testing approach should be used (M. C. Neale & Kendler, 1995).

The use of a common pathway model in Paper 1 but not in paper 3

In Paper 1, we used a common pathway model to estimate genetic and environmental contributions to AVPD and DEPD corrected for measurement errors. The ideal method in Paper 3 would perhaps be to use the same approach. We had several reasons for not doing this. Firstly, this approach would result in a highly parameterized and complicated model. Secondly, we found in Paper 1 that the DPQ had less specificity for capturing PDs, and semi-structured interview measures are generally regarded as the best method for this purpose. Thirdly, by only using the interview measure our study would be more compatible with other twin studies on PDs, as using common pathway models unfortunately is still quite rare for PDs. Lastly, although the heritabilities most probably would have increased, we would argue that the correlations between the genetic factors for PDs and LTSL would not have changed.

5.1.6 Limitations

Representativeness

Our findings are based on a sample of young, adult Norwegian twins. The results may thus not be representative for other age or ethnic groups. Heritability estimates are dependent on the population studied and the time point when the phenotypes were measured. Further, if twins are different from other non-twins, this would be a problem for the external validity of the results. Twins are found to differ from non-twins in some manners, such as having a lower birth weight and higher prevalence of prematurity, birth complications and language delay (Kendler & Prescott, 2006). However, twins have not been found to differ from non-twins in their liability to psychiatric disorders (Kendler et al., 1996; Rutter & Redshaw, 1991) or personality (Johnson et al., 2002). To what extent twins differ from non-twins in liability to medical benefits is not known, but our sample had a somewhat lower prevalence of DP than the general Norwegian population in this age group (Norgeshelsa, 2013b). This discrepancy is probably not explained by our sample being twins, but rather by the typical trend of respondents of questionnaires having higher socioeconomic background, higher education etc, and that those who are worse off tend not to participate. As we had included rehabilitation allowances in our LTSL variable our sample had a somewhat higher prevalence of LTSL than the general population in the same age group (Norgeshelsa, 2013a).

There was a high rate of attrition from the Q2 sample to the interview sample. Non-response and attrition in epidemiological studies is often linked to low socioeconomic status and poorer health, resulting in samples that may not be representative for the population. The attrition from Q2 to the interview study has been investigated, and out of 45 predictors, including 22 mental health related variables, only age and monozygosity predicted participation in the interview study (Tambs et al., 2009). More importantly, non-random attrition may lead to biased estimates of genetic and environmental effects (Heath et al., 1998). However, the Tambs et al. study did not find evidence for differences in the covariation structure for a large number of variables between participants and non-participants.

Overlap in time between PD measures and LTSL

In Paper 3, we investigated which of the PDs measures from 1999 to 2004 that were associated with LTSL, recorded from 1998 to 2008. For this purpose, the PD measures should ideally not overlap in time with the LTSL measure. However, approximately 90% of the participants were interviewed before the end of 2002. PDs also have an onset in adolescence or early adulthood (APA, 2000) and are measured as “during the last 5 years”. We therefore feel confident that PDs

preceded LTSL in the observation period and that it was reasonable to use the LTSL variable that included information for the whole time-span available. Should we censored out LTSL before 2004, there would have been a large loss of statistical power which would probably have resulted in fewer significantly associated PDs.

5.2 Interpretation of the findings

5.2.1 Heritability of PDs and medical benefits

That PDs are heritable have been more or less established, both indirectly, through studies of personality traits (Bouchard & Loehlin, 2001; Jang, Livesley, & Vernon, 1996), and through a few studies on the whole range of DSM-III (Torgersen et al., 2000) and DSM-IV PDs (Kendler et al., 2008), as well as cluster-wise for the DSM-IV PDs (Kendler et al., 2006; Kendler et al., 2007; Reichborn-Kjennerud et al., 2004; Torgersen et al., 2008; Torgersen et al., 2012). Less established is the size of the heritability. The first study that was conducted on PDs measured by a structured interview found great variability in the heritability estimates for DSM-III PDs (Torgersen et al., 2000). The sample for this study was small (92 MZ and 129 DZ twins), and also based on twin pairs where at least one of the twins had been treated for a mental disorder. It is thus reasonable to assume that the estimates may have been subject to random fluctuations in the data, and also may not be representative for the population. Subsequent studies have been based on large population-based samples. The first wave of these studies did not correct for measurement error, and found the heritability of all DSM-IV PDs (excluding those in the appendix) to range between 0.21 and 0.41 (Kendler et al., 2008; Kendler et al., 2006; Reichborn-Kjennerud et al., 2007; Torgersen et al., 2008). With the use of common pathway models, the heritability of cluster A and B PDs increased to vary between 0.55 and 0.72 (Kendler et al., 2007; Torgersen et al., 2012), a finding that underscores the importance of taking measurement errors into account when interpreting heritability estimates.

In Paper 1, we continued this line of research, and investigated the heritability of cluster C PDs corrected for measurement errors. Due to the lack of items in the DPQ that overlapped with the SIDP-IV criteria for obsessive-compulsive PD, we were not able to investigate reliable genetic and environmental contributions to this PD and thus omitted it from the paper. The most important finding in this paper was that the heritability increased for both AVPD (from 0.35 in the previous study to 0.64 in this study) and DEPD (from 0.31 in the previous study to 0.66 in the present study) when correcting for measurement error. Unique environmental influences accounted for the rest of the variance in AVPD and DEPD. The finding challenges the assumed etiology of these PDs. While we previously thought that most of the variance in AVPD and

DEPD was explained by environmental factors not shared between twins in a pair, we now find evidence in favor of genetic variance being the most important contributor to the liability. The finding that genes are so important for the development of these disorders implies that clinicians should strive to obtain a thorough family history from patients that display symptoms of these disorders. That genes are more influential than environmental factors should not be interpreted to mean that these disorders are not treatable. A review study has found strong evidence for PDs being treatable, both with psychodynamic and cognitive behavioral therapy (Leichsenring & Leibing, 2003). Our findings further underscore the importance of using several measures or time-points to obtain reliable estimates. As it is relatively rare to use more than one measurement and time-point, we believe that measurement error should be taken into account when interpreting estimates from studies on other phenotypes as well.

The heritability of medical benefits has been largely unexplored. The first study on heritability of DP was conducted on a Finnish sample, which found the heritability to range between 0.24 and 0.48, depending on diagnosis (Harkonmäki et al., 2008). A more recent twin study on a Swedish sample found the heritability of DP due to different diagnoses to range between 0.27 to 0.49 (Narusyte et al., 2011). Interestingly, both studies found that the heritability decreased with increasing age, thus demonstrating that environmental factors increased in importance for the DP liability as the participants grew older. For sick leave, only one study had investigated the heritability, and found it to be 0.36 for a point prevalence of LTSL (Svedberg et al., 2012). Of these three studies, only the Swedish study on DP found evidence any sex differences, in this case expressed as different pathways to DP for males and females.

In Paper 2, we investigated genetic and environmental contributions to both LTSL and DP. In line with previous studies, we also found evidence of substantial heritability, estimated to 0.49 for LTSL and 0.66 for DP, and no significant contributions from shared environmental effects. Our estimates are higher than previously found, which I believe to some extent can be explained by the age differences between the samples. The longer follow-up time for DP in the previous studies, as well as the differences in how we constructed the sick leave measures, may also to some extent explain why the estimates differed. Despite the higher prevalence of LTSL and DP for females compared to males, as well as the DZU correlations being lower than the geometric mean for the like-sexed DZ twins, we did not find evidence of significant sex differences in the twin models. If sex effects were present that we did not have power to detect, this could have inflated the heritability estimates. However, the previous studies, with the exception of the Swedish study on DP, also did not find evidence of sex differences, despite having substantially larger sample sizes than the present study.

5.2.2 Interpretation and implications of the heritability of LTSL and DP

In the paper on LTSL and DP, we have strived to underscore that having a family history of granted medical benefits does not imply a gloomy future, despite the high heritability of these phenomena. High heritability does not imply that an individual is bound to express the phenotype (Neisser et al., 1996). This is a serious misunderstanding which in the worst case scenario could lead to passivity. Knowing the heritability of a phenotype does not mean that the mechanisms through which the genetic effects operate are known. Whether or not a phenotype will be expressed is not only dependent on the genotypic potential, but on the complex interplay between genes and environmental exposures.

The most natural explanation of why LTSL and DP are heritable is that they are often elicited by mental and somatic symptoms or disorders that are heritable. However, some of the symptoms or disorders that are set as reasons for being granted either LTSL or DP can also be present in individuals that do not receive medical benefits. Therefore, it is likely that other characteristics influence the propensity to receive medical benefits, such as pain tolerance, locus of control, self-efficacy and personality. Differences in these characteristics may render some individuals less able to cope with mental or somatic symptoms. This is in line with the reasoning in previous papers, where the heritability of divorce and stressful life events was argued to be explained to some extent by personality characteristics (Kendler et al., 1993; McGue & Lykken, 1992). This hypothesis has later been explored in a bivariate twin analysis including personality as measured by the Multidimensional Personality Questionnaire and divorce, where it was found that genetic factors for personality could account for 30-40% of the heritability of divorce (Jockin et al., 1996).

In sum, we can only speculate which traits underlie the obtained heritability estimates for LTSL and DP. To gain more knowledge on this issue, futures studies should include additional variables associated with these outcomes. Given the current lack of knowledge on which factors that can account for the heritability of LTSL and DP, it is difficult to use the results from this study to suggest specific interventions that can aim at reducing the risk for LTSL and DP.

5.2.3 Environmental risk factors for LTSL and DP

The estimates from Paper 2 and 3 showed that approximately half of the variance in LTSL, and in paper 2, about one third of the variance in DP, could be attributed to environmental effects not shared between twins in a pair (E). Although our studies cannot be used to answer which specific environmental factors that affect liability to LTSL and DP, many phenotypic studies (as mentioned under 1.3.6) have found associations between various social and environmental

exposures and these outcomes. Interestingly, in Paper 2 we found an almost complete overlap in the environmental risk factors for LTSL and DP. This finding corresponds well with the studies on risk factors for medical benefits, as there is considerable overlap in the risk factors found to be associated with LTSL and DP. For instance, low level of education (Ahola et al., 2011; Eshoj et al., 2001; Ropponen et al., 2011), unemployment (Biering-Sorensen et al., 1999; Eshoj et al., 2001), hard physical work (Ahola et al., 2011; Eshoj et al., 2001; Krokstad et al., 2002; Steenstra et al., 2005), and low social support and social isolation (Albertsen et al., 2007; Steenstra et al., 2005) have all been found to predict LTSL and DP in separate studies. It should be noted that many of these conditions have been found to also be influenced by genetic factors, which underscores the value of genetically informative studies (e.g. Bergeman et al., 1990; Branigan et al., 2013; Tambs et al., 1989).

5.2.4 Social transmission

As mentioned in 1.3.6, it has been speculated in the media that propensity to medical benefits could be transferred through other people in an individual's network, such as family and friends. Studies with large sample sizes have also found evidence for increased risk of DP in cases where parents or neighbours were recipients (Kristensen et al., 2004; Rege et al., 2012). The Kristensen et al. study investigated DP within families, and hence the results could be due to genetic confounding. In Paper 2, the issue of genetic confounding was resolved by using a sample of twins. Here, we explored whether social transmission was present, both through testing for sibling interaction and for shared environmental effects. We did not find significant effects for neither of these, and thus there was no evidence for social transmission in our sample. Instead, the familial aggregation of LTSL and DP was entirely due to genetic effects. The absence of significant effects could be due to limited statistical power. There is thus a need for more studies before we can conclude whether social transmission affect propensity to receive medical benefits or not.

5.2.5 Transition from LTSL to DP

LTSL has been found to be a risk factor for subsequent DP in previous studies (Ahola et al., 2011; Gjesdal et al., 2005). These findings were supported in Paper 2, where the phenotypic correlation between these variables was 0.86 (0.85-0.88, 95% CI). A strong phenotypic correlation was expected, as all of the individuals in our sample that were granted DP had also had at least one episode of LTSL. The important question is thus not whether there is an association or not, but rather why some individuals transit from LTSL to DP. No previous studies have investigated this question through a genetically informative design. In Paper 2, we were able to explore further

what the association between LTSL and DP was due to. We found that the phenotypic correlation could be delineated into both genetic and environmental risk factors that overlapped to a strong degree. Although the environmental correlation was highest, genes common to both phenotypes explained most of the phenotypic correlation. The results suggest that mainly the same risk factors apply to both LTSL and DP. However, we also found evidence for a genetic factor of moderate size that was not shared in common for LTSL and DP. This specific genetic factor, as well as extreme scores on the genetic factor common to LTSL and DP, could be the key to explain why some transit to DP whereas others return to work. The results from Paper 2 thus extend the knowledge on the etiological basis of the association between LTSL and DP, but more studies are needed to understand what the specific genetic factor that separate LTSL from DP reflects.

5.2.6 PDs as risk factors for LTSL

Common mental disorders have been found to be risk factors for LTSL (Henderson et al., 2011; Knudsen et al., 2013; Shiels et al., 2004; Stansfeld et al., 1995) but there have been a lack of studies on how PDs relate to LTSL. As it has been found that extreme scores on some normal personality traits are associated with short-and long-term sick leave (Stormer & Fahr, 2013; Vlasveld et al., 2012), and that PDs are associated with impaired functioning on several domains (Nakao et al., 1992; Skodol et al., 2002) it is reasonable to assume that PDs are also related to LTSL.

In Paper 3 we investigated the association between 10 DSM-IV PDs and LTSL as well as the degree to which genetic and environmental factors could account for the association. The two PDs included in Paper 1, AVPD and DEPD, were along with histrionic and obsessive-compulsive PD significantly associated with LTSL. After adjusting for other significant PDs, however, only schizotypal, paranoid and borderline PD remained significantly associated with LTSL. Thus, it seems that it is the odd and eccentric and the emotional and unstable clusters that increase risk for LTSL, whereas the PDs in the anxious and fearful cluster are significant only through traits shared with other PDs. These findings resembles those of previous studies, where DSM-IV schizotypal and borderline (Skodol et al., 2002) and DSM-III schizotypal, paranoid and borderline (Nakao et al., 1992) were the most impairing PDs. The overall association between the selected PDs and LTSL was modest, as 90% of the variance in LTSL was unrelated to PDs. The remaining 10% was almost entirely due to shared genetic factors. Genetic contributions to schizotypal, paranoid and borderline PD accounted for 20% of the heritability of LTSL. This is a modest number, but when considering all possible phenotypes that could influence the liability to LTSL, this proportion is of a considerable size. As the association was mainly due to one genetic factor

shared in common for the three PDs and LTSL, it seems to be the combined effect of these PDs that is most important for liability to LTSL. Interestingly, the pattern of results in Paper 3 resembles those of a previous study of personality and divorce. Divorce is, as discussed under 1.1.4, another phenotype that has also mainly been studied within the social science field. The aforementioned study found that the association between personality and divorce was mainly due to shared genetic factors, and 30-42% of the heritability of divorce could be attributed to genetic contributions for the personality assessment (Jockin et al., 1996). In line with Jockin et al. on divorce, we also recommend more extensive twin studies including a broader array of variables to account for the rest of the heritability of LTSL.

We were surprised that our results did not support a causal hypothesis, but rather that the association between PDs and LTSL was due to genetic confounding. An indication of a causal association would be expected, as PDs are associated with symptomatic suffering and health complaints (Noren et al., 2007) as well as frequent attendance to general practice (Moran et al., 2001). Participation in the work force also requires interaction with other people, which may be challenging for individuals with schizotypal, paranoid or borderline PD, at least according to the DSM-IV criteria. However, it is possible that the early onset of PDs could delay or obstruct occupational development (Grilo & McGlashan, 2005) and thus that individuals with the most severe PDs never seek employment, making them non-eligible to LTSL.

Despite the modest overlap in variance for PDs and LTSL and the absence of evidence of a causal association, we would hesitate to interpret the results to mean that PDs are not important for LTSL. The absence of significant E-correlations does not necessarily imply that these do not exist. When inspecting the CIs for the genetic and environmental correlations, we see that the upper CIs for the environmental correlations are close to the lower CIs for the genetic correlations. Thus, with a larger sample, it is reasonable to assume that both significant genetic and environmental correlations could have been obtained, which would have indicated a causal association. The absence of indications of a causal pathway between PDs and LTSL must therefore be interpreted with caution.

5.2.7 Confidence in the findings

A central question that may be asked in all types of research is - how confident can we be that our findings reflect the true nature of the phenomena we have studied? The answer depends on the sample size and representativeness, the reliability and validity of the measures, as well as the appropriateness of the statistical analyses and the validity of the assumptions behind these, as discussed under section 5.1. The approaches we have used to study PDs, LTSL and DP have

several strengths, but there are also some limitations. Therefore, the estimates we have found are not 100% precise, as reflected in the confidence intervals. Despite the uncertainty in the estimates, I believe we can be confident in the overall picture drawn through this line of research, namely that both genetic and environmental factors are important to explain liability to PDs, LTSL and DP. That previous studies on the same phenotypes have found similar results further increases confidence in the findings. This is however, far from the conclusion drawn by critics like Joseph, who claims that invalidity of one or more of the assumptions behind the classical twin model implies that genetics do not contribute to variability in mental disorders (Joseph, 2012). Invalidity of assumptions does imply that heritability estimates should be adjusted to some extent (how much could be calculated from simulation studies), but it certainly does not imply that genes have no impact at all.

5.3 Future studies

The findings from the current study indicate directions that could be pursued in future studies.

In Paper 3, we found that PDs explained 20% of the heritability of LTSL. As an extension on this, one could include other essential variables to better account for the heritability. For instance by including the most common somatic and/or mental disorders, or by investigating the influence of normal personality, and other personality traits such as locus of control and pain sensitivity.

As mentioned in section 5.1.5, it would also be valuable to fit a common pathway model to PDs and LTSL. It is possible that PDs would be able to account for more of the heritability in LTSL if measurement error could be corrected for. Further, I believe that it could be advantageous to collapse several PDs into one factor or sum score, as it has been found that global functioning decrease with increasing number of PD criteria met (Nakao et al., 1992). This approach would yield more statistical power and could thus increase the likelihood of obtaining a significant E-correlation, which is expected for a causal association.

Many studies have investigated the effects different social and environmental risk factors have on LTSL (as discussed under 1.3.6). As an extension of this, it could be valuable to investigate to what extent genetic factors interact with stressors such as low social support or physically demanding work.

In line with studies conducted on stressful life events (Kendler et al., 1993; Plomin et al., 1990), it would be interesting to separate out LTSL and DP that resulted from extrinsic versus intrinsic influences. Based on previous findings (Kendler et al., 1993; Plomin et al., 1990) it could be hypothesized that medical benefits caused by extrinsic factors that an individual has less

control of would have lower heritability than the intrinsic types. It could for instance be that the heritability for sick leave and disability due to accidents is lower than that due to diagnoses that have developed over time. However, being prone to accidents is also heritable, although it is probably less heritable to be hit by a falling piano than to be involved in a base-jumping accident.

5.4 Conclusion

By using a large, population-based sample of young adult Norwegian twins, we have provided new insights on the heritability of PDs, LTSL and DP, and on the genetic and environmental structure of the association between LTSL and DP, and between PDs and LTSL. The main findings were that; AVPD and DEPD have a higher heritability than previously assumed; liability to both LTSL and DP is substantially influenced by genetic factors; there is a strong overlap between the genetic and environmental risk factors to LTSL and DP; and that the association between schizotypal, paranoid and borderline PD and LTSL is mainly due to genetic factors. The heavy hand of genetics found for the included phenotypes should not be interpreted as an admission of failure for possible interventions. That PDs have high heritability does not make them less treatable. For LTSL and DP, the findings may constitute a stepping stone to provide more insights on where interventions should be aimed at to reduce the inflow to these medical benefits. A recommendable strategy for this aim could be to further investigate risk factors for LTSL and DP with genetically informative designs.

REFERENCES

Ahola, K., Virtanen, M., Honkonen, T., Isometsä, E., Aromaa, A., & Lönnqvist, J. (2011). Common mental disorders and subsequent work disability: A population-based Health 2000 Study. *Journal of Affective Disorders, 134*, 365-372.

Akaike, H. (1987). Factor analysis and AIC. *Psychometrica, 52*, 317-332.

Akselsen, A., Lien, S., & Siverstøl, Ø. (2007). FD-trygd. List of variables. Oslo: Statistics Norway.

Albertsen, K., Lund, T., Christensen, K. B., Kristensen, T. S., & Villadsen, E. (2007). Predictors of disability pension over a 10-year period for men and women. *Scandinavian Journal of Public Health, 35*(1), 78-85.

Alexanderson, K., Hensing, G. , & Borg, K. (2005). Sickness absence with low-back, shoulder, or neck diagnoses-a 12 year follow-up regarding sickness absence and disability pension. *Work, 25*, 115-124.

Allebeck, P., & Mastekaasa, A. (2004). Chapter 5. Risk factors for sick leave - general studies. [Review]. *Scandinavian Journal of Public Health, 32*, 49-108.

Andersen, L. L., Clausen, T., Mortensen, O. S., Burr, H., & Holtermann, A. (2012). A prospective cohort study on musculoskeletal risk factors for long-term sickness absence among healthcare workers in eldercare. *International Archives of Occupational and Environmental Health, 85*(6), 615-622.

Andersson, L., Wiles, N., Lewis, G., Brage, S., & Hensing, G. (2006). Disability pension for psychiatric disorders: Regional differences in Norway 1988-2000. *Nordic Journal of Psychiatry, 60*(4), 255-262.

APA. (2000). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Association.

Appelberg, K., Romanov, K., Heikkila, K., Honkasalo, M. L., & Koskenvuo, M. (1996). Interpersonal conflict as a predictor of work disability: A follow-up study of 15,348 Finnish employees. *Journal of Psychosomatic Research, 40*(2), 157-167.

Benirschke, K. (2009). The Monozygotic Twinning Process, the Twin-twin Transfusion Syndrome and Acardiac Twins. *Placenta, 30*(11), 923-928.

Bergeman, C. S., Plomin, R., Pedersen, N. L., McClearn, G. E., & Nesselroade, J. R. (1990). Genetic and environmental influences on social support - The Swedish adoption twin study of aging. *Journals of Gerontology, 45*(3), 101-106.

Besseling, J. J. M., Rijkenberg, A. M., Andriessen, S., & de Vos, E. L. (2008). Increasing Use of Social Benefits by Young People with Chronic Illness or Disability in the Netherlands. *Rehabilitation, 47*(6), 366-371.

Biering-Sorensen, F., Lund, J., Hoydalsmo, O. J., Darre, E. M., Deis, A., Kryger, P., & Muller, C. F. (1999). Risk indicators of disability pension - A 15 year follow-up study. *Danish Medical Bulletin, 46*(3), 258-262.

Boker, M.S., Neale, M. C., Maes, H., Wilde, M., Spiegel, M., Brick, T., Spies, J. , Estabrook, R., Kenny, S., Bates, T. , Mehta, P., & Fox, J. (2011). OpenMx: An open source extended structural equation modeling framework. *Psychometrica, 76*(2), 306-317.

Bollen, K.A. (1989). *Structural equations with latent variables*. New York: Wiley.

Bouchard, T. J., & Loehlin, J. C. (2001). Genes, evolution, and personality. [Review]. *Behavior Genetics, 31*(3), 243-273.

Bouchard, T. J., & McGue, M. (2003). Genetic and environmental influences on human psychological differences. *Journal of Neurobiology, 54*(1), 4-45.

Branigan, A. R., McCallum, K. J., & Freese, J. (2013). Variation in the Heritability of Educational Attainment: An International Meta-Analysis. *Social Forces, 92*(1), 109-140.

Bronisch, T., & Mombour, W. (1998). The modern assessment of personality disorders - Part 2: Reliability and validity of personality disorders. *Psychopathology, 31*(6), 293-301.

Bultmann, U., Christensen, K. B., Burr, H., Lund, T., & Rugulies, R. (2008). Severe depressive symptoms as predictor of disability pension: a 10-year follow-up study in Denmark. *European Journal of Public Health, 18*(3), 232-234.

Caspi, A. (2000). The child is father of the man: Personality continuities from childhood to adulthood. *Journal of Personality and Social Psychology, 78*(1), 158-172.

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., Taylor, A., & Poulton, R. (2002). Role of genotype in the cycle of violence in maltreated children. *Science, 297*(5582), 851-854.

Cloninger, C. R. (2000). A practical way to diagnosis personality disorder: A proposal. *Journal of Personality Disorders, 14*(2), 99-108.

Conte, R.C, Plutchik, R, Karasu, T.B, & Jerret, I. (1980). A self-report borderline scale. Discriminative validity and preliminary norms. *Journal of Nervous & Mental Disease, 168*, 428-435.

Coolidge, F. L., Thede, L. L., & Jang, K. L. (2001). Heritability of personality disorders in childhood: A preliminary investigation. [Article]. *Journal of Personality Disorders, 15*(1), 33-40.

Coventry, W. L., & Keller, M. C. (2005). Estimating the extent of parameter bias in the classical twin design: A comparison of parameter estimates from extended twin-family and classical twin designs. *Twin Research and Human Genetics, 8*(3), 214-223.

Defries, J. C., & Fulker, D. W. (1985). Multiple regression analysis of twin data. *Behavior Genetics, 15*, 467-473.

Dekkers-Sanchez, P. M., Hoving, J. L., Sluiter, J. K., & Frings-Dresen, M. H. W. (2008). Factors associated with long-term sick leave in sick-listed employees: a systematic review. [Review]. *Occupational and Environmental Medicine, 65*(3), 153-157.

Derogatis, L.R., Lipman, R.S., Rickels, K., Uhlenluth, E.H., & Covi, L. (1974). The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behavioral Science, 19*(1), 1-15.

Dobson, A. J. (2002). *An Introduction to Generalized Linear Models*. London: Chapman & Hall/CRC.

Dominicus, Annica, Skrondal, Anders, Gjessing, Håkon, Pedersen, Nancy, & Palmgren, Juni. (2006). Likelihood Ratio Tests in Behavioral Genetics: Problems and Solutions. *Behavior Genetics, 36*(2), 331-340.

Drake, R. E., & Vaillant, G. E. (1985). A validity study of Axis II of DSM-III. *American Journal of Psychiatry, 142*(5), 553-558.

Dunn, E. C., Uddin, M., Subramanian, S. V., Smoller, J. W., Galea, S., & Koenen, K. C. (2011). Research Review: Gene-environment interaction research in youth depression - a systematic review with recommendations for future research. *Journal of Child Psychology and Psychiatry, 52*(12), 1223-1238.

Duyme, M., Dumaret, A. C., & Tomkiewicz, S. (1999). How can we boost IQs of "dull children"?: A late adoption study. *Proceedings of the National Academy of Sciences of the United States of America, 96*(15), 8790-8794.

Eaton, N. R., Krueger, R. F., South, S. C., Simms, L. J., & Clark, L. A. (2011). Contrasting prototypes and dimensions in the classification of personality pathology: evidence that dimensions, but not prototypes, are robust. *Psychological Medicine, 41*(6), 1151-1163.

Eaves, L. (1976). A model for sibling effects in man. *Heredity, 36*(2), 205-214.

Eshoj, P., Jepsen, J. R., & Nielsen, C. V. (2001). Long-term sickness absence - risk indicators among occupationally active residents of a Danish county. *Occupational Medicine-Oxford, 51*(5), 347-353.

Eysenck, H.J. (1947). *Dimensions of personality*. London: Routledge & Kegan Paul.

Falconer, D.S., & Mackay, T.F.C. (1996). *Introduction to quantitative genetics (4th edition)*. Harlow, UK: Pearson

Folketrygdloven [National Insurance Act], Lovdata (retrieved from: http://www.lovdata.no/all/nl-19970228-019.html), LOV-1997-02-28-19 Stat. (1997).

Foulds, G.A. (1965). *Personality and Personal Illness*. London: Tavistock.

Fowler, J. H., Baker, L. A., & Dawes, C. T. (2008). Genetic variation in political participation. *American Political Science Review, 102*(2), 233-248.

Friborg, O., Martinussen, M., Kaiser, S., Overgard, K. T., & Rosenvinge, J. H. (2013). Comorbidity of personality disorders in anxiety disorders: A meta-analysis of 30 years of research. [Review]. *Journal of Affective Disorders, 145*(2), 143-155.

Gjesdal, S., Haug, K., & Ringdal, P. R. (2005). The risk of disability pension among young persons on long-term sick leave. *Tidsskrift for Den Norske Lægeforeningen*(125), 1801-1805.

Grant, B. F., Chou, S. P., Goldstein, R. B., Huang, B., Stinson, F. S., Saha, T. D., Smith, S. M., Dawson, D. A., Pulay, A. J., Pickering, R. P., & Ruan, W. J. (2008). Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: Results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. [Review]. *Journal of Clinical Psychiatry, 69*(4), 533-545.

Gravseth, H. M., Bjerkedal, T., Irgens, L. M., Aalen, O. O., Selmer, R., & Kristensen, P. (2007). Life course determinants for early disability pension: a follow-up of Norwegian men and women born 1967-1976. *European Journal of Epidemiology, 22*(8), 533-543.

Grilo, C. M., & McGlashan, T. H. (2005). Course and outcome of personality disorders. In J. M. Oldham, A. E. Skodol & D. S. Bender (Eds.), *Textbook of personality disorders* (pp. 103-115). Washington D.C.: American Psychiatric Publishing.

Guo, G., & Wang, J. M. (2002). The mixed or multilevel model for behavior genetic analysis. *Behavior Genetics, 32*(1), 37-49.

Ha, I. D., Lee, Y., & Pawitan, Y. (2007). Genetic mixed linear models for twin survival data. *Behavior Genetics, 37*(4), 621-630.

Harkonmaki, K., Korkeila, K., Vahtera, J., Kivimaki, M., Suominen, S., Sillanmaki, L., & Koskenvuo, M. (2007). Childhood adversities as a predictor of disability retirement. *Journal of Epidemiology and Community Health, 61*(6), 479-484.

Harkonmäki, K., Silventoinen, K., Levälahti, E., Pitkäniemi, J., Huunan-Seppälä, A., Klaukka, T., Koskenvuo, M., & Kaprio, J. (2008). The genetic liability to disability retirement: A 30-year follow-up study of 24,000 Finnish twins. *Plos One, 3*(10).

Harris, J. R., Magnus, P., & Tambs, K. (2006). The Norwegian Institute of Public Health twin program of research: an update. *Twin Research and Human Genetics, 9*(6), 858-864.

Harris, J. R., Magnus, P., & Tambs, K. . (2002). The Norwegian Institute of Public Health Twin Panel: A description of the sample and program of research. *Twin Research, 5*, 415-423.

Haukenes, I., Gjesdal, S., Rortveit, G., Riise, T., & Maeland, J. G. (2012). Women's higher likelihood of disability pension: the role of health, family and work. A 5-7 years follow-up of the Hordaland Health Study. [Article]. *Bmc Public Health, 12*. doi: 720 10.1186/1471-2458-12-720

Heath, A. C., Madden, P. A. F., & Martin, N. G. (1998). Assessing the effects of cooperation bias and attrition in behavioral genetic research using data-weighting. *Behavior Genetics, 28*(6), 415-427.

Heijbel, B., Josephson, M., Jensen, I., Stark, S., & Vingard, E. (2006). Return to work expectation predicts work in chronic musculoskeletal and behavioral health disorders: Prospective study with clinical implications. *Journal of Occupational Rehabilitation, 16*(2), 173-184.

Heim, A., & Westen, D. (2005). Theories of personality and personality disorders. In J. M. Oldham, A. E. Skodol & D. S. Bender (Eds.), *Textbook of personality disorders* (pp. 17-33). Washington D.C.: American Psychiatric Publishing.

Helgeland, M.I., Kjelsberg, E., & Torgersen, S. (2005). Continuities between emotional and disruptive behavior disorders in adolescence and personality disorders in adulthood. *American Journal of Psychiatry, 162*, 1941-1947.

Hemingway, H., Shipley, M., Stansfeld, S., Shannon, H., Frank, J., Brunner, E., & Marmot, M. (1999). Are risk factors for atherothrombotic disease associated with back pain sickness absence? The Whitehall II study. [Article]. *Journal of Epidemiology and Community Health, 53*(4), 197-203.

Henderson, M., Harvey, S. B., Overland, S., Mykletun, A., & Hotopf, M. (2011). Work and common psychiatric disorders. [Review]. *Journal of the Royal Society of Medicine, 104*(5), 198-207.

Hensing, G. (2004). Chapter 4. Methodological aspects in sickness-absence research. *Scandinavian Journal of Public Health, 32*, 44-48.

Hensing, G., Andersson, L., & Brage, S. (2006). Increase in sickness absence with psychiatric diagnosis in Norway: a general population-based epidemiologic study of age, gender and regional distribution. *Bmc Medicine, 4*. doi: 19 10.1186/1741-7015-4-19

Hultin, H., Lindholm, C., & Moller, J. (2012). Is There an Association between Long-Term Sick Leave and Disability Pension and Unemployment beyond the Effect of Health Status? - A Cohort Study. *Plos One, 7*(4). doi: e35614. 10.1371

Hur, Y. M. (2003). Assortative mating for personality traits, educational level, religious affiliation, height, weight, and body mass index in parents of a Korean twin sample. *Twin Research, 6*(6), 467-470.

Ihlebaek, C., Brage, S., & Eriksen, H. R. (2007). Health complaints and sickness absence in Norway, 1996-2003. *Occupational Medicine, 57*, 43-49.

Jang, K. L., Livesley, W. J., & Vernon, P. A. (1996). Heritability of the big five personality dimensions and their facets: a twin study. *Journal of Personality, 64*(3), 577-591.

Jang, K. L., Livesley, W. J., Vernon, P. A., & Jackson, D. N. (1996). Heritability of personality disorder traits: a twin study. *Acta Psychiatrica Scandinavica, 94*(6), 438-444.

Jansson, C., Alexanderson, K., Kecklund, G., & Akerstedt, T. (2013). Clinically diagnosed insomnia and risk of all-cause and diagnosis-specific sickness absence: A nationwide Swedish prospective cohort study. *Scandinavian Journal of Public Health, 41*(7), 712-721.

Jockin, V., McGue, M., & Lykken, D. T. (1996). Personality and divorce: A genetic analysis. *Journal of Personality and Social Psychology, 71*(2), 288-299.

Johnson, W., Krueger, R.F., Bouchard, T.J., & McGue, M. (2002). The personalities of twins: Just ordinary folks. *Twin Research, 5*, 125-131.

Joseph, J. (2012). The "Missing Heritability" of Psychiatric Disorders: Elusive Genes or Non-Existent Genes? *Applied Developmental Science, 16*(2), 65-83.

Keller, L. M., Arvey, R. D., Dawis, R. V., Bouchard, T. J., & Segal, N. L. (1992). Work values - Genetic and environmental influences. *Journal of Applied Psychology, 77*(1), 79-88.

Kendler, K. S., Aggen, S. H., Czajkowski, N., Roysamb, E., Tambs, K., Torgersen, S., Neale, M. C., & Reichborn-Kjennerud, T. (2008). The Structure of Genetic and Environmental Risk Factors for DSM-IV Personality Disorders A Multivariate Twin Study. *Archives of General Psychiatry, 65*(12), 1438-1446.

Kendler, K. S., Aggen, S. H., Knudsen, G. P., Roysamb, E., Neale, M. C., & Reichborn-Kjennerud, T. (2011). The Structure of Genetic and Environmental Risk Factors for Syndromal and Subsyndromal Common DSM-IV Axis I and All Axis II Disorders. *American Journal of Psychiatry, 168*(1), 29-39.

Kendler, K. S., Kessler, R. C., Walters, E. E., MacLean, C., Neale, M. C., Heath, A. C., & Eaves, L. J. (1995). Stressful life events, genetic liability, and onset of an episode of major depression in women. *Am J Psychiatry, 152*(6), 833-842.

Kendler, K. S., Neale, M., Kessler, R., Heath, A., & Eaves, L. (1993). A twin study of recent life events and difficulties. *Archives of General Psychiatry, 50*(10), 789-796.

Kendler, K. S., Pedersen, N. L., Farahmand, B. Y., & Persson, P. G. (1996). The treated incidence of psychotic and affective illness in twins compared with population expectation: a study in the Swedish Twin and Psychiatric Registries. *Psychological Medicine, 26*(6), 1135-1144.

Kendler, K.S., Czajkowski, Nikolai, Tambs, Kristian, Torgersen, Svenn, Aggen, Steven H., Neale, Michael C., & Reichborn-Kjennerud, Ted. (2006). Dimensional representations of DSM-IV Cluster A personality disorders in a population-based sample of Norwegian twins: A multivariate study. *Psychological Medicine, 36*(11), 1583-1591.

Kendler, K.S., Myers, J., Torgersen, S., Neale, M. C., & Reichborn-Kjennerud, T. (2007). The heritability of cluster A personality disorders assessed by both personal interview and questionnaire. *Psychological Medicine, 37*(5), 655-665.

Kendler, K.S., & Prescott, C.A. (2006). *Genes, environment, and psychopathology: Understanding the causes of psychiatric and substance use disorders*. New York: Guilford Press.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions' of DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry, 62*(6), 593-602.

Khoury, M. J., Beaty, T. H., & Cohen, B. (1993). *Fundamentals of Genetic Epidemiology*. New York: Oxford University Press.

Kivimaki, M., Ferrie, J. E., Hagberg, J., Head, J., Westerlund, H., Vahtera, J., & Alexanderson, K. (2007). Diagnosis-specific sick leave as a risk marker for disability pension in a Swedish population. *Journal of Epidemiology and Community Health, 61*(10). doi: 915 10.1136/jech.2006.055426

Knudsen, A. K., Harvey, S. B., Mykletun, A., & Overland, S. (2013). Common mental disorders and long-term sickness absence in a general working population. The Hordaland Health Study. *Acta Psychiatrica Scandinavica, 127*(4), 287-297.

Knudsen, A. K., Overland, S., Hotopf, M., & Mykletun, A. (2012). Lost Working Years Due to Mental Disorders: An Analysis of the Norwegian Disability Pension Registry. *Plos One, 7*(8).

Knudsen, A. K., Skogen, J. C., Harvey, S. B., Stewart, R., Hotopf, M., & Moran, P. (2012). Personality disorders, common mental disorders and receipt of disability benefits: evidence from the British National Survey of Psychiatric Morbidity. *Psychological Medicine, 42*(12), 2631-2640.

Koopmans, P. C., Roelen, C. A. M., Bultmann, U., Hoedeman, R., van der Klink, J. J. L., & Groothoff, J. W. (2010). Gender and age differences in the recurrence of sickness absence due to common mental disorders: a longitudinal study. *Bmc Public Health, 10*. doi: 426 10.1186/1471-2458-10-426

Korkeila, J., Oksanen, T., Virtanen, M., Salo, P., Nabi, H., Pentti, J., Vahtera, J., & Kivimaki, M. (2011). Early retirement from work among employees with a diagnosis of personality disorder compared to anxiety and depressive disorders. *European Psychiatry, 26*(1), 18-22.

Krause, N., Lynch, J., Kaplan, G. A., Cohen, R. D., Goldberg, D. E., & Salonen, J. T. (1997). Predictors of disability retirement. *Scandinavian Journal of Work Environment & Health, 23*(6), 403-413.

Kristensen, P., Bjerkedal, T., & Brevik, J. I. (2004). Long term effects of parental disability: A register based life course follow-up of Norwegians born in 1967–1976. *Norsk Epidemiologi, 14*(1), 97-105.

Krokstad, S., Johnsen, R., & Westin, S. (2002). Social determinants of disability pension: a 10-year follow-up of 62 000 people in a Norwegian county population. *International Journal of Epidemiology, 31*(6), 1183-1191.

Lazare, A., Klerman, G.L., & Armor, D.J. (1966). Oral, obsessive, and hysterical personality patterns. An investigation of psychoanalytic concepts by means of factor analysis. *Archives of General Psychiatry, 14*, 624-630.

Leichsenring, F., & Leibing, E. (2003). The effectiveness of psychodynamic therapy and cognitive behavior therapy in the treatment of personality disorders: A meta-analysis. [Review]. *American Journal of Psychiatry, 160*(7), 1223-1232.

Lenzenweger, M. F., Lane, M. C., Loranger, A. W., & Kessler, R. C. (2007). DSM-IV personality disorders in the National Comorbidity Survey Replication. *Biological Psychiatry, 62*(6), 553-564.

Livesley, W. J. (1998). Suggestions for a framework for an empirically based classification of personality disorder.[see comment]. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie, 43*(2), 137-147.

Livesley, W. J., & Jang, K. L. (2008). The behavioral genetics of personality disorder. *Annual Review of Clinical Psychology, 4*, 23.

Livesley, W. J., Jang, K. L., & Vernon, P. A. (1998). Phenotypic and genetic structure of traits delineating personality disorder. *Archives of General Psychiatry, 55*(10), 941-948.

Maczulskij, T. (2013). Employment sector and pay gaps: Genetic and environmental influences. *Labour Economics, 23*, 89-96.

Maes, H. H. M., Neale, M. C., Kendler, K. S., Hewitt, J. K., Silberg, J. L., Foley, D. L., Meyer, J. M., Rutter, M., Simonoff, E., Pickles, A., & Eaves, L. J. (1998). Assortative mating for major psychiatric diagnoses in two population-based samples. *Psychological Medicine, 28*(6), 1389-1401.

Magnus, P., Berg, K., & Nance, W. E. (1983). Predicting zygosity in Norwegian twin pairs born 1915-1960. *Clinical Genetics, 24*, 103-112.

Maher, B. A., & Maher, W. B. (1994). Personality and psychopathology - A historical perspective. *Journal of Abnormal Psychology, 103*(1), 72-77.

Markon, K. E., Krueger, R. F., Bouchard, T. J., & Gottesman, II. (2002). Normal and abnormal personality traits: Evidence for genetic and environmental relationships in the Minnesota Study of Twins Reared Apart. *Journal of Personality, 70*(5), 661-693.

McCrae, R. R., & Costa, P. T. (1997). Personality trait structure as a human universal. *American Psychologist, 52*(5), 509-516.

McCrae, R. R., Lockenhoff, C. E., & Costa, P. T. (2005). A step toward DSM-V: Cataloguing personality-related problems in living. *European Journal of Personality, 19*(4), 269-286.

McCrae, R.R, & Costa, Jr Paul T. . (1990). *Personality in Adulthood*. New York, NY: Guilford Press.

McDermut, W., & Zimmerman, M. (2005). Assessment instruments and standardized evaluation. In J. M. Oldham, A. E. Skodol & D. S. Bender (Eds.), *Textbook of personality disorders* (pp. 89-101). Washington D.C.: American Psychiatric Publishing.

McGue, M., & Lykken, D. T. (1992). Genetic influence on risk of divorce. *Psychological Science, 3*(6), 368-373.

Michon, H. W. C., ten Have, M., Kroon, H., van Weeghel, J., de Graav, R., & Schene, A. H. (2008). Mental disorders and personality traits as determinants of impaired work functioning. *Psychological Medicine, 38*(11), 1627-1637.

Mittal, V. A., Ellman, L. M., & Cannon, T. D. (2008). Gene-Environment Interaction and Covariation in Schizophrenia: The Role of Obstetric Complications. *Schizophrenia Bulletin, 34*(6), 1083-1094.

Modestin, J., & Villiger, C. (1989). Follow-up study on borderline versus non-borderline personality disorders. *Comprehensive Psychiatry, 30*(3), 236-244.

Morabia, A. (2011). History of the modern epidemiological concept of confounding. *Journal of Epidemiology and Community Health, 65*(4), 297-300.

Moran, P., Rendu, A., Jenkins, R., Tylee, A., & Mann, A. (2001). The impact of personality disorder in UK primary care: a 1-year follow-up of attenders. [Article]. *Psychological Medicine, 31*(8), 1447-1454.

Moum, T. (1998). Mode of administration and interviewer effects in self-reported symptoms of anxiety and depression. [Review]. *Social Indicators Research, 45*(1-3), 279-318.

Mykletun, A., Overland, S., Dahl, A. A., Krokstad, S., Bjerkeset, O., Glozier, N., & Aaro, L. E. (2006). A population-based cohort study of the effect of common mental disorders on disability pension awards. *American Journal of Psychiatry, 163*(8), 1412-1418.

Nakao, K., Gunderson, J. G., Phillips, K. A., Tanaka, N., Yorifuji, K., Takaishi, J., & Nishimura, T. (1992). Functional impairment in personality disorders. *Journal of Personality Disorders, 6*(1), 24-33.

Narusyte, J., Ropponen, A., Silventoinen, K., Alexanderson, K., Kaprio, J., Samuelsson, A., & Svedberg, P. (2011). Genetic Liability to Disability Pension in Women and Men: A Prospective Population-Based Twin Study. *Plos One, 6*(8).

NAV. (2013). Uførepensjon [Disability pension] Retrieved December 3rd, 2013, from https://www.nav.no/Om+NAV/Tall+og+analyse/Jobb+og+helse/Uf%C3%B8repensjon

Neale, B. M., & Rijsdijk, F. (2005). Further considerations for power in sibling interaction models. *Behavior Genetics, 35*(5), 671-674.

Neale, M. C. (2003). A finite mixture distribution model for data collected from twins. *Twin Research, 6*(3), 235-239.

Neale, M. C., Eaves, L. J., & Kendler, K. S. (1994). The power of the classical twin study to resolve variation in threshold traits. *Behavior Genetics, 24*(3), 239-258.

Neale, M. C., & Kendler, K. S. (1995). Models of comorbidity for multifactorial disorders. *Am J Hum Genet, 57*(4), 935-953.

Neale, M. C., Roysamb, E., & Jacobson, K. (2006). Multivariate genetic analysis of sex limitation and G x E interaction. *Twin Research & Human Genetics: the Official Journal of the International Society for Twin Studies, 9*(4), 481-489.

Neale, M.C., Boker, M.S., Xie, G., & Maes, H.H. (2003). *Mx: statistical Modelling (6th ed.)*: VCU Box 900126 Richmond, VA 23298: Department of Psychiatry.

Neale, M.C., & Maes, H.H. (2000). *Methodology for genetic studies of twins and families*. Dordrecht: Kluwer Akademic Publisher B.V.

Neisser, U., Boodoo, G., Bouchard, T. J., Boykin, A. W., Brody, N., Ceci, S. J., Halpern, D. F., Loehlin, J. C., Perloff, R., Sternberg, R. J., & Urbina, S. (1996). Intelligence: Knowns and unknowns. *American Psychologist, 51*(2), 77-101.

Noren, K., Lindgren, A., Haellstom, T., Thormaehlen, B., Vinnars, B., Wennberg, P., Weinryb, R. M., & Barber, J. P. (2007). Psychological distress and functional impairment in patients with personality disorders. *Nordic Journal of Psychiatry, 61*(4), 260-270.

Norgeshelsa. (2013a). Statistikkbank: Sykefravær [Statistics: sickness absence rate] Retrieved October 1st, 2013, from http://www.norgeshelsa.no/norgeshelsa/?language=en

Norgeshelsa. (2013b). Statistikkbank: Uførepensjon [Statistics: Disability pension] Retrieved October 1st, 2013, from http://www.norgeshelsa.no/norgeshelsa/?language=en

NOU. (Norwegian Official Reports 2000:27). Sykefravær og uførepensjonering - Et inkluderende arbeidsliv [Sickness absence and disability pensioning - a labour market for all]. Oslo: Norway.

NOU. (Norwegian Official Reports 2007:4). Ny uførestønad og ny alderspensjon til uføre [New disability pension and age related retirement pensions due to disability]. Oslo: Norway.

NOU. (Norwegian Official Reports 2010:13). Arbeid for helse - Sykefravær og utstøting i helse- og omsorgssektoren [Work for health - Sick leave and exlusion in the health and care services]. Oslo: Norway.

OECD. (2006). Sickness, Disability and Work: Breaking the Barriers - Norway, Poland and Switzerland Vol.1. Paris: OECD Publishing.

OECD. (2010a). Health at a Glance: Europe 2010. Paris: OECD Publishing.

OECD. (2010b). Sickness, disability and work. Breaking the barriers. A synthesis of findings across OECD countries. Paris: OECD Publishing.

Oldham, J. M. (2005). Personality disorders: Recent history and future directions. In J. M. Oldham, A. E. Skodol & D. S. Bender (Eds.), *Textbook of personality disorders* (pp. 3-17). Washington D.C.: American Psychiatric Publishing.

Oldham, J. M., Skodol, A. E., Kellman, H. D., Hyler, S. E., Rosnick, L., & Davies, M. (1992). Diagnosis of DSM-III-R personality disorders by 2 structured interviews - Patterns of comorbidity. *American Journal of Psychiatry, 149*(2), 213-220.

Ose, S. O. (2010). Kunnskap om sykefravær: nye norske bidrag [Knowledge on sickness absence: New Norwegian contributions]. SINTEF: Trondheim.

Overland, S., Harvey, S. B., Knudsen, A. K., Mykletun, A., & Hotopf, M. (2012). Widespread pain and medically certified disability pension in the Hordaland Health Study. *European Journal of Pain, 16*(4), 611-620.

Painter, J. N., Medland, S.J., Montgomery, G. W., & Hall, J. G. (2006). Twins and Twinning. In D. L. Rimoin, J. M. Connor, R. E. Pyeritz & B. R. Korf (Eds.), *Emery and Rimoin's Principles and Practice of Medical Genetics* (5th edition ed., pp. 1-20). London: Churchill Livingstone.

Pfohl, B. Blum, & Zimmerman, M. (1995). *Structured Interview for DSM-IV Personality (SIDP-IV).* Iowa City: University of Iowa, Department of Psychiatry.

Pietikainen, S., Silventoinen, K., Svedberg, P., Alexanderson, K., Huunan-Seppala, A., Koskenvuo, K., Koskenvuo, M., Kaprio, J., & Ropponen, A. (2011). Health-Related and Sociodemographic Risk Factors for Disability Pension due to Low Back Disorders A 30-Year Prospective Finnish Twin Cohort Study. *Journal of Occupational and Environmental Medicine, 53*(5), 488-496.

Pilkonis, P. A., Heape, C. L., Proietti, J. M., Clark, S. W., McDavid, J. D., & Pitts, T. E. (1995). The reliability and validity of 2 structured diagnostic interviews for personality disorders. *Archives of General Psychiatry, 52*(12), 1025-1033.

Plomin, R., Defries, J. C., & Loehlin, J. C. (1977). Genotype-environment interaction and correlation in analysis of human-behavior. *Psychological Bulletin, 84*(2), 309-322.

Plomin, R., DeFries, J. D., McClearn, G. E., & McGuffin, P. (2001). *Behavioral Genetics* (4th ed.). New York: Worth Publishers.

Plomin, R., Lichtenstein, P., Pedersen, N., McClearn, G.E., & Nesselroade, J.R. (1990). Genetic influences on life events during the last half of the life span. *Psychological Aging, 5*(25-30).

R. (2005). A Language and Environment for Statistical Computing, from http://www.r-project.org/

Rai, D., Kosidou, K., Lundberg, M., Araya, R., Lewis, G., & Magnusson, C. (2012). Psychological distress and risk of long-term disability: population-based longitudinal study. *Journal of Epidemiology and Community Health, 66*(7), 586-592.

Rege, M., Telle, K., & Votruba, M. (2012). Social Interaction Effects in Disability Pension Participation: Evidence from Plant Downsizing. *Scandinavian Journal of Economics, 114*(4), 1208-1239.

Regjeringen. (2013). *The Norwegian Social Insurance Scheme*. Retrieved from http://www.regjeringen.no/en/dep/ad/doc/veiledninger_brosjyrer/2013/the-norwegian-social-insurance-scheme-20.html?id=716026.

Reichborn-Kjennerud, T., Bulik, C. M., Tambs, K., & Harris, J. R. (2004). Genetic and environmental influences on binge eating in the absence of compensatory behaviors: a population-based twin study. *International Journal of Eating Disorders, 36*(3), 307-314.

Reichborn-Kjennerud, T., Czajkowski, N., Neale, M. C., Orstavik, R. E., Torgersen, S., Tambs, K., Roysamb, E., Harris, J. R., & Kendler, K. S. (2007). Genetic and environmental influences on dimensional representations of DSM-IV cluster C personality disorders: a population-based multivariate twin study. *Psychological Medicine, 37*(5), 645-653.

Rietveld, M. J. H., Posthuma, D., Dolan, C. V., & Boomsma, D. I. (2003). ADHD: Sibling interaction or dominance: An evaluation of statistical power. *Behavior Genetics, 33*(3), 247-255.

Rijsdijk, F.V., & Sham, P. C. (2002). Analytic approaches to twin data using structural equation models. *Briefings in Bioinformatics, 3*(2), 119-133.

Ropponen, A., Silventoinen, K., Svedberg, P., Alexanderson, K., Koskenvuo, K., Huunan-Seppala, A., Koskenvuo, M., & Kaprio, J. (2011). Health-related risk factors for disability pensions due to musculoskeletal diagnoses: A 30-year Finnish twin cohort study. *Scandinavian Journal of Public Health, 39*(8), 839-848.

Ropponen, A., Svedberg, P., Kalso, E., Koskenvuo, M., Silventoinen, K., & Kaprio, J. (2013). A prospective twin cohort study of disability pensions due to musculoskeletal diagnoses in relation to stability and change in pain. *Pain, 154*(10), 1966-1972.

Rothbart, M. K., Ahadi, S. A., & Evans, D. E. (2000). Temperament and personality: Origins and outcomes. *Journal of Personality and Social Psychology, 78*(1), 122-135.

Roysamb, E., Kendler, K. S., Tambs, K., Orstavik, R. E., Neale, M. C., Aggen, S. H., Torgersen, S., & Reichborn-Kjennerud, T. (2011). The Joint Structure of DSM-IV Axis I and Axis II Disorders. *Journal of Abnormal Psychology, 120*(1), 198-209.

Rutter, M. (2006). *Genes and Behavior: Nature-Nurture Interplay Explained*. Oxford: Blackwell Publishing.

Rutter, M., & Redshaw, J. (1991). Annotation - Growing up as a twin - Twin-singleton differences in psychological development. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 32*(6), 885-895.

Samuel, D. B., & Widiger, T. A. (2004). Clinicians' personality descriptions of prototypic personality disorders. *Journal of Personality Disorders, 18*(3), 286-308.

Samuelsson, A., Ropponen, A., Alexanderson, K., Lichtenstein, P., & Svedberg, P. (2012). Disability Pension Among Swedish-Twins Prevalence Over 16 Years and Associations With Sociodemographic Factors in 1992. *Journal of Occupational and Environmental Medicine, 54*(1), 10-16.

Seivewright, H., Tyrer, P., & Johnson, T. (2004). Persistent social dysfunction in anxious and depressed patients with personality disorder. *Acta Psychiatrica Scandinavica, 109*(2), 104-109.

Shiels, C., Gabbay, M. B., & Ford, F. M. (2004). Patient factors associated with duration of certified sickness absence and transition to long-term incapacity. [Article]. *British Journal of General Practice, 54*(499), 86-91.

Sinokki, M., Hinkka, K., Ahola, K., Gould, R., Puukka, P., Lonnqvist, J., & Virtanen, M. (2010). Social Support as a Predictor of Disability Pension: The Finnish Health 2000 Study. *Journal of Occupational and Environmental Medicine, 52*(7), 733-739.

Skillgate, E., Vingard, E., Josephson, M., Holm, L. W., & Alfredsson, L. (2009). Is smoking and alcohol consumption associated with long-term sick leave due to unspecific back or neck pain among employees in the public sector? Results of a three-year follow-up cohort study. *Journal of Rehabilitation Medicine, 41*(7), 550-556.

Skodol, A. E., Gunderson, J. G., McGlashan, T. H., Dyck, I. R., Stout, R. L., Bender, D. S., Grilo, C. M., Shea, M. T., Zanarini, M. C., Morey, L. C., Sanislow, C. A., & Oldham, J. M. (2002). Functional impairment in patients with schizotypal, borderline, avoidant, or obsessive-compulsive personality disorder. *American Journal of Psychiatry, 159*(2), 276-283.

Smith, G. D., & Phillips, A. N. (1992). Confounding in epidemiologic studies - why independent effects may not be all they seem. *British Medical Journal, 305*(6856), 757-759.

Sorensen, H. T., Sabroe, S., & Olsen, J. (1996). A framework for evaluation of secondary data sources for epidemiological research. *International Journal of Epidemiology, 25*(2), 435-442.

South, S. C., & DeYoung, N. J. (2013). Behavior Genetics of Personality Disorders: Informing Classification and Conceptualization in DSM-5. *Personality Disorders-Theory Research and Treatment, 4*(3), 270-283.

SPSS. (2009). *PASW Statistics 17.0 Command Syntax Reference*. Chicago: SPSS Inc.

SSB. (2013a). Statistics Norway Statbank: Sickness absence, Q2 2013 Retrieved December 3rd, 2013, from https://www.ssb.no/en/arbeid-og-lonn/statistikker/sykefratot

SSB. (2013b). Statistics Norway: About the historical event database FD-Trygd (Forløpsdatabasen Trygd) Retrieved October 28th 2013, from http://www.ssb.no/a/english/mikrodata_en/datasamling/fdtrygd_en.html

Stansfeld, S., Feeney, A., Head, J., Canner, R., North, F., & Marmot, M. (1995). Sickness absence for psychiatric illness - The Whitehall-II study. *Social Science & Medicine, 40*(2), 189-197.

Stapelfeldt, C. M., Jensen, C., Andersen, N. T., Fleten, N., & Nielsen, C. V. (2012). Validation of sick leave measures: self-reported sick leave and sickness benefit data from a Danish

national register compared to multiple workplace-registered sick leave spells in a Danish municipality. *Bmc Public Health, 12*. doi: 661 10.1186/1471-2458-12-661

Steenstra, I. A., Verbeek, J. H., Heymans, M. W., & Bongers, P. M. (2005). Prognostic factors for duration of sick leave in patients sick listed with acute low back pain: a systematic review of the literature. [Review]. *Occupational and Environmental Medicine, 62*(12), 851-860.

Stormer, S., & Fahr, R. (2013). Individual determinants of work attendance: evidence on the role of personality. *Applied Economics, 45*(19), 2863-2875.

Susser, E., & Bresnahan, M. (2001). Origins of epidemiology. In M. Weinstein, A. I. Hermalin & M. A. Stoto (Eds.), *Population Health and Aging: Strengthening the Dialogue between Epidemiology and Demography* (Vol. 954, pp. 6-18).

Suvisaari, J., Aalto-Setala, T., Tuulio-Henriksson, A., Harkanen, T., Saarni, S. I., Perala, J., Schreck, M., Castaneda, A., Hintikka, J., Kestila, L., Lahteenmaki, S., Latvala, A., Koskinen, S., Marttunen, M., Aro, H., & Lonnqvist, J. (2009). Mental disorders in young adulthood. *Psychological Medicine, 39*(2), 287-299.

Svedberg, P., Ropponen, A., Alexanderson, K., Lichtenstein, P., & Narusyte, J. (2012). Genetic susceptibility to sickness absence is similar among women and men: Findings from a Swedish twin cohort. *Twin Research and Human Genetics, 15*(5), 642-648.

Svedberg, P., Ropponen, A., Lichtenstein, P., & Alexanderson, K. (2010). Are self-report of disability pension and long-term sickness absence accurate? Comparisons of self-reported interview data with national register data in a Swedish twin cohort. *Bmc Public Health, 10*.

Tambs, K., Ronning, T., Prescott, C. A., Kendler, K. S., Reichborn-Kjennerud, T., Torgersen, S., & Harris, J. R. (2009). The Norwegian Institute of Public Health twin study of mental health: examining recruitment and attrition bias. *Twin Research and Human Genetics, 12*(2), 158-168.

Tambs, K., Sundet, J. M., Magnus, P., & Berg, K. (1989). Genetic and environmental contributions to the covariance between occupational status, educational attainment, and IQ - A study of twins. *Behavior Genetics, 19*(2), 209-222.

Teare, M.D. (Ed.). (2011). *Genetic Epidemiology (Methods in Molecular Biology)*. New York: Humana Press.

Tesser, A. (1993). The importance of heritability in psychological research - The case of attitudes. *Psychological Review, 100*(1), 129-142.

Torgersen, S. (1980). Hereditary-environmental differentiation of general neurotic, obsessive, and impulsive hysterical personality traits. *Acta Geneticae Medicae et Gemellologiae, 29*, 193-207.

Torgersen, S. (1984). Genetic and Nosological Aspects of Schizotypal and Borderline Personality Disorders: A Twin Study. *Archives of General Psychiatry, 41*, 546-554.

Torgersen, S., Czajkowski, N., Jacobson, K., Reichborn-Kjennerud, T., Roysamb, E., Neale, M. C., & Kendler, K. S. (2008). Dimensional representations of DSM-IV cluster B personality disorders in a population-based sample of Norwegian twins: a multivariate study. *Psychological Medicine, 38*(11), 1617-1625.

Torgersen, S., Kringlen, E., & Cramer, V. (2001). The prevalence of personality disorders in a community sample. *Archives of General Psychiatry, 58*(6), 590-596.

Torgersen, S., Lygren, S., Oien, P. A., Skre, I., Onstad, S., Edvardsen, J., Tambs, K., & Kringlen, E. (2000). A twin study of personality disorders. *Comprehensive Psychiatry, 41*(6), 416-425.

Torgersen, S., Myers, J., Reichborn-Kjennerud, T., Røysamb, E., Kubarych, T., & Kendler, K.S. (2012). The heritability of Cluster B personality disorders assessed both by personal interview and questionnaire. *Journal of Personality Disorders, 26*(6), 848-866.

Trull, Timothy J., & Durrett, Christine A. (2005). Categorical and dimensional models of personality disorder. *Annual Review of Clinical Psychology, 1*(1), 355-380.

Turkheimer, E. (2000). Three laws of behavior genetics and what they mean. *Current Directions in Psychological Science, 9*(5), 160-164.

Vaez, M., Rylander, G., Nygren, A., Asberg, M., & Alexanderson, K. (2007). Sickness absence and disability pension in a cohort of employees initially on long-term sick leave due to psychiatric disorders in Sweden. *Social Psychiatry and Psychiatric Epidemiology, 42*(5), 381-388.

Vingard, E., Lindberg, P., Josephson, M., Voss, M., Heijbel, B., Alfredsson, L., Stark, S., & Nygren, A. (2005). Long-term sick-listing among women in the public sector and its associations with age, social situation, lifestyle, and work factors: A three-year follow-up study. *Scandinavian Journal of Public Health, 33*(5), 370-375.

Vlasveld, M.C., van der Feltz-Cornelis, C.M., Anema, J.R., van Mechelen, W., Beekman, A.T., van Marwijk, H.W., & Penninx, B.W. (2012). The Associations Between Personality Characteristics and Absenteeism: A Cross-Sectional Study in Workers With and Without Depressive and Anxiety Disorders. *Journal of Occupational Rehabilitation, 23*, 309-317.

Westen, D. (1997). Divergences between clinical and research methods for assessing personality disorders: Implications for research and the evolution of axis II. *American Journal of Psychiatry, 154*(7), 895-903.

WHO. (1992). *ICD-10 Classifications of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization.

WHO. (2013). Health Topics: Epidemiology. http://www.who.int/topics/epidemiology/en/ Retrieved September 5, 2013

Widiger, T. A., & Costa, P. T. (1994). Personality and personality disorders. *Journal of Abnormal Psychology, 103*(1), 78-91.

Widiger, T. A., Livesley, W. J., & Clark, L. A. (2009). An Integrative Dimensional Classification of Personality Disorder. [Review]. *Psychological Assessment, 21*(3), 243-255.

Widiger, T. A., & Mullins-Sweatt, S. N. (2005). Categorical and dimensional models of personality disorders. In J. M. Oldham, A. E. Skodol & D. S. Bender (Eds.), *Textbook of personality disorders* (pp. 35-53). Washington D.C.: American Psychiatric Publishing.

Yanez, N. D., Kronmal, R. A., & Shemanski, L. R. (1998). The effects of measurement error in response variables and tests of association of explanatory variables in change models. *Statistics in Medicine, 17*(22), 2597-2606.

Zimmerman, M., & Coryell, W. (1989). DSM-III personality disorder diagnoses in a non-patient sample - demographic correlates and co-morbidity. *Archives of General Psychiatry, 46*(8), 682-689.

Zimmermann, M. (1994). Diagnosing personality disorders. A review of issues and research methods. *Archives of General Psychiatry, 51*, 225-245.

Østby, K. A., Czajkowski, N., Knudsen, G.P., Gjerde, L. C., Kendler, K.S., Ørstavik, R.E., & Reichborn-Kjennerud, T. (submitted). Personality disorders are an important risk factor for disability pensioning *Social Psychiatry & Psychiatric Epidemiology*

PAPER 1

Gjerde, L. C., Czajkowski, N., Røysamb, E., Ørstavik, R. E., Knudsen, G. P., Østby, K., Torgersen, S., Myers, J., Kendler, K. S. & Reichborn-Kjennerud, T. (2012). The heritability of avoidant and dependent personality disorder assessed by personal interview and questionnaire. *Acta Psychiatrica Scandinavica* **126**, 448-457.

PAPER 2

Gjerde, L. C., Knudsen, G. P., Czajkowski, N., Gillespie, N., Aggen, S. H., Røysamb, E., Reichborn-Kjennerud, T., Tambs, K., Kendler, K. S. & Ørstavik, R. E. (2013). Genetic and environmental contributions to long-term sick leave and disability pension: a population-based study of young adult Norwegian twins. *Twin Research and Human Genetics* **16,** 759-766.

Twin Research and Human Genetics
Volume 16 ▌ Number 4 ▌ pp. 759–766 ▌ © The Authors 2013 ▌ doi:10.1017/thg.2013.36

Genetic and Environmental Contributions to Long-Term Sick Leave and Disability Pension: A Population-Based Study of Young Adult Norwegian Twins

Line C. Gjerde,[1] Gun Peggy Knudsen,[1] Nikolai Czajkowski,[1,4] Nathan Gillespie,[5] Steven H. Aggen,[5] Espen Røysamb,[1,4] Ted Reichborn-Kjennerud,[1,2,3] Kristian Tambs,[1] Kenneth S. Kendler,[5,6] and Ragnhild E. Ørstavik[1]

[1]Department of Mental Health, Norwegian Institute of Public Health, Oslo, Norway
[2]Institute of Psychiatry, University of Oslo, Oslo, Norway
[3]Department of Epidemiology, Columbia University, New York, NY, USA
[4]Department of Psychology, University of Oslo, Oslo, Norway
[5]Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA
[6]Departments of Psychiatry and Human and Molecular Genetics, Virginia Commonwealth University, Richmond, VA, USA

Although exclusion from the workforce due to long-term sick leave (LTSL) and disability pension (DP) is a major problem in many Western countries, the etiology of LTSL and DP is not well understood. These phenomena have a strong association as most patients receiving DP have first been on LTSL. However, only a few of those on LTSL end up with DP. The present study aimed to investigate the common and specific genetic and environmental risk factors for LTSL and DP. The present study utilizes a population-based sample of 7,710 young adult twins from the Norwegian Institute of Public Health Twin Panel, which has been linked to the Historical-Event Database (FD-Trygd; 1998–2008). Univariate and bivariate twin models were fitted to determine to what degree genetic and environmental factors contribute to variation in LTSL and DP. The estimated heritabilities of LTSL and DP were 0.49 and 0.66, respectively. There was no evidence for shared environmental or sex-specific factors. The phenotypic-, genetic-, and non-familial environmental correlations between the variables were 0.86, 0.82, and 0.94, respectively. Our results indicate that familial transmission of LTSL and DP is due to genetic and not environmental factors. The risk factors contributing to LTSL and DP were mainly shared, suggesting that what increases risk for LTSL also increases risk for DP. However, a non-negligible part of the genetic variance was not shared between the variables, which may contribute to explaining why some progress from LTSL to DP, whereas others return to work.

■ **Keywords:** long-term sick leave, disability pension, twin studies

Medical benefits for sickness absence and disability put a large economic burden on society (Moncrieff & Pomerleau, 2000; Organisation for Economic Co-operation and Development (OECD), 2003). Most patients on long-term sick leave (LTSL) return to work, but in some cases LTSL leads to disability pension (DP) and thus often permanent exclusion from the workforce. According to Norwegian data (Gjesdal et al., 2005), 9% of patients aged less than 40 years who were on LTSL for the first time were granted DP five years later. The risk was particularly high for LTSL due to mental disorders (11% of women and 24% of men). The societal and personal costs are particularly high when young people are granted DP. In order to understand why some young adults transit from LTSL to DP whereas others return to work, it is important to investigate common and specific risk factors for LTSL and DP.

In most industrialized countries, sick leave benefits are granted based on disease or injury resulting in reduced work capacity (Soderberg & Alexanderson, 2003). In Norway, sick leave for the first 16 days is paid by the employers, and

RECEIVED 19 December 2012; ACCEPTED 30 April 2013. First published online 7 June 2013.

ADDRESS FOR CORRESPONDENCE: Line C. Gjerde, Norwegian Institute of Public Health, Box 4404, Nydalen N-0403, Oslo, Norway. E-mail: line.gjerde@fhi.no

thereafter mandatorily covered by the Norwegian Insurance Scheme (NIS) for a period of up to 52 weeks (Gjesdal & Bratberg, 2003). Due to varying definitions and processes of sick leave certification, it is difficult to compare sick leave prevalence across countries. However, a recent report has investigated the trajectories of sick leave in a subset of European countries from 1990 to 2008 and found that sick leave spells are increasing in countries like Norway, Denmark, and Finland (EUROSTAT Statistics; Ose, 2010).

In Norway, individuals aged 18 to 67 years whose work capacity is reduced by more than 50% as a cause of illness or injury are entitled to DP after relevant treatment and rehabilitation (Norwegian Official Reports (NOU), 2000). For working individuals, a sick leave period of one year is most common before DP is granted. A DP can be graded or granted full-time. In Norway between 2004 and 2010, there was also the possibility of being granted a time-limited DP. The granting of DP has steadily increased during the last decade in OECD countries (OECD, 2003), especially in younger populations (Besseling et al., 2008), where mental disorders are the most common cause for DP (Mykletun et al., 2006).

We are only aware of one study that has investigated genetic liability to LTSL (Svedberg et al., 2012). In this study, which was based on a twin sample aged 43–65 and a point prevalence of LTSL, the heritability was 0.36. Knowledge about genetic and environmental contributions to LTSL in younger populations is thus currently lacking. Genetic and environmental contributions to DP have been investigated in a Finnish and Swedish twin sample (Harkonmäki et al., 2008, Narusyte et al., 2011). The heritability ranged from 0.24 to 0.48, depending on the type of diagnosis. The genetic effect was highest in younger cohorts, and, in the Swedish study (Narusyte et al., 2011) for the group granted DP based on a mental disorder. No study that we know of has investigated the association between genetic and environmental risk factors for LTSL and DP.

Musculoskeletal and mental disorders are the most common causes for LTSL and DP (Knudsen et al., 2012, Ose, 2010), and genetic factors are important for the liability to these disorders (Battie et al., 2007, Kendler & Prescott, 2006). In Norway, the increase in LTSL and DP does not, however, seem to be followed by a corresponding increase in the prevalence of the aforementioned disorders (Ihlebaek et al., 2007, Ose, 2010). Thus, factors apart from those influencing the risk for sickness per se can influence liability to LTSL and DP. Whether phenomena such as social transmission can explain the increasing trend is not known. If such an effect is mediated through family members — for instance, through attitudes toward medical benefits — we would expect it to appear as a significant shared environment effect in twin data (C, explained below). Another way of revealing social transmission is to test for sibling interaction effects. Sibling interaction is present if the phenotype of one sibling influences the behavior of another (Eaves, 1976).

The aim of the present study is to investigate the common and specific genetic and environmental contributions to the liability to LTSL and DP in young adult twins by using biometric twin modelling.

Materials and Methods

Sample

The sample for the current study originated from the Norwegian Institute of Public Health Twin Panel (NIPHTP). The twins are identified through information in the national Medical Birth Registry, which was established on January 1, 1967. The selected participants for the current study were those who had taken part in either a large questionnaire study in 1998 and/or in an interview study a few years later. By using twins who had participated in the previous studies, we were able to identify their zygosity, which was necessary for the twin analyses. The NIPHTP has been used previously in several studies (Tambs et al., 2009), and is described thoroughly elsewhere (Harris et al., 2006). By using the unique national identification numbers issued to all Norwegians at birth, the data obtained from the twins who participated in the questionnaire and interview studies was linked to the following registries at Statistics Norway: The Norwegian National Education Database (NUDB), The Historical-Event Database (FD-Trygd), and the Income Register. This constituted a sample of 7,710 twins, born between 1967 and 1979.

FD-Trygd is a database containing data from the entire population (1992 and onwards) from several sources: registries at Statistics Norway; the Norwegian Labour and Welfare Organisation and the Employment Directorate; and the Norwegian Tax Administration. The database contains information regarding all social security benefits, including, for example, sickness benefits, social assistance, rehabilitation allowance, DP, and unemployment benefits (Akselsen et al., 2007). As the register data at Statistics Norway is updated annually, we have obtained a detailed, longitudinal dataset on the 7,710 young adult twins, including annual information on the variables listed above from 1998 to 2008. The mean age at the start of follow-up in 1998 was 25.6 years. The 7,710 twins included 3,108 pairs and 1,494 singletons. Of the complete pairs, 492 were monozygotic (MZ) males, 354 dizygotic (DZ) males, 759 MZ females, 607 DZ females, and 896 opposite sex twins. Of the singletons, 210 were MZ males, 286 DZ males, 176 MZ females, 218 DZ females, and 592 opposite sex twins. Twelve singletons were excluded from the analyses due to missing information on zygosity. In the sample, 42.1% were males, and 97.5% were employed at some point during the observation period.

Zygosity was initially determined using questionnaire items previously shown to classify correctly more than 97% of the twin pairs (Magnus et al., 1983), followed by DNA analyses on a subgroup of the sample. The discrepancy between classification based on the questionnaire and DNA

markers implied an expected misclassification rate of approximately 2% for the whole sample, which is unlikely to bias our results (Neale, 2003).

The linkage of data from NIPHTP with registries at Statistics Norway was approved by the Regional Ethical Committee.

Measures

After 52 weeks of sick leave, an individual who is unable to work is sometimes granted medical and/or vocational rehabilitation in order to undergo treatment or training aimed at regaining work ability (NOU, 2000). We defined LTSL as sickness absence of >16 days (the minimal sick leave period that is recorded in our dataset). We also included periods of rehabilitation in the LTSL variable, as this reflects a similar condition to LTSL. We separately summed up the total number of days of sickness absence, rehabilitation, and working days (defined as being registered as employed) in the 10-year follow-up period either up to the time of granted DP, death, or 2008. The LTSL variable was then defined as a ratio (0–100%) between the cumulative number of sick days and rehabilitation days over the cumulative number of potential working days. The LTSL proportion was further divided into four categories of approximately equal sizes, from 0 to 3, as this variable was positively skewed; 0 comprised those individuals without LTSL in the period, 1 comprised those with up to 5% LTSL in the period, 2 comprised those with 5–15% LTSL in the period, and 3 comprised those with >15% LTSL in the period. Absence of LTSL (LTSL = 0) was only defined in individuals eligible for sickness allowance, that is, at least one employment period had to be registered. A total of 187 twins were censored out from the LTSL and DP variables either due to death (34), no employment in the period (143), or for being granted DP before 2000 (10).

The DP variable comprises all twins who were granted DP before or during the follow-up period of 1998 to 2008. All types of DP were included, regardless of time limitation or grading. The information on DP was scored as follows: 0 = no DP, 1 = at least one period of graded (40–90%) DP, and 2 = only full-time (100%) DP.

Statistical Analyses

Ordinal data analyses. We used the raw ordinal data analysis option in the OpenMx software (Boker et al., 2011). This approach is based on the central limit theorem, assuming that ordered categories are imprecise indicators of an unobserved, normally distributed liability, which can be estimated as thresholds that discriminate between the categories (Falconer, 1965, Tallis, 1962). Analogous to tests of mean- and variance homogeneity for continuous data, ordinal data analysis allows us to test the equality of threshold distributions within twin pairs across sex and zygosity. Moreover, by including both complete and incomplete data, the method has the advantage of increasing the accuracy of the estimation of the thresholds, thereby improving estimation of polychoric correlations. To validate the estimation of polychoric correlations, bivariate normality tests were conducted for the variables in R (R Development Core Team, 2005).

Model fitting. In the classical twin design (Jinks & Fulker, 1970; Martin & Eaves, 1977), individual differences in liability are assumed to arise from additive genetic (A), shared environment (C), and non-shared environment (E) sources. As MZ twins share all, and DZ twins share on average half of their segregating genes, based on theory A this would tend to make MZ twins correlate twice as high as DZ twins. C is defined as environmental factors that contribute to similarity between twins, and is further assumed to have an equal effect on MZ and DZ twins. E is by definition not shared between twins in a pair, and hence does not contribute to twin similarity. E also contains measurement error. The influence of each of these factors on the variables can be estimated using structural equation modelling (SEM; Neale & Maes, 2000). Liability-threshold models were fitted using full information maximum likelihood (FIML) as estimation procedure to the raw data in OpenMx. If minimum regularity conditions are satisfied, the difference in -2 times log likelihood (Δ - 2LL) is asymptotically χ^2 distributed, which allows testing for significant deterioration in χ^2 for nested submodels. If the difference in χ^2 is non-significant, the simpler, restricted model is preferred over the more highly parameterized and complex model. In addition, as an index of parsimony, Akaike Information Criterion (AIC), calculated as χ^2 - 2df (Akaike, 1987), was also used to select the best fitting model. Preferred models are those with the lowest AIC value.

Univariate analyses. Univariate ACE models allowing for both qualitative and quantitative sex differences were first fitted to the data. Qualitative sex differences involve different genetic and/or environmental effects for males and females on the same trait, while quantitative sex effects involve the same genetic and environmental structure, but with different effect sizes for the sexes. If the observed opposite-sex DZ correlation is less than the like-sex DZ correlation, this suggests the possibility of qualitative sex differences. It is possible to test for qualitative sex differences by letting the parameter that specifies genetic correlation between the opposite-sex DZ twin pairs to vary between 0 and 0.5. Since this test (general sex limitation model) is restricted to opposite-sex pairs only, it is adequately powered only in quite large samples. Testing for quantitative sex difference (common sex limitation model) is done by allowing the A, C, and E parameter effects to differ across male and female twins and then compare the fit of this model with a model constraining the parameters to be equal across sex (no sex limitation model). After testing for sex effects, it is common to run submodels testing for significance of the A and C parameters by fixing selected parameters to be 0 in

TABLE 1

Polychoric Correlations With 95% Confidence Intervals for LTSL and DP by Zygosity

	LTSL	DP
MZ males	0.52 (0.42–0.60)	0.94 (0.79–0.99)
DZ males	0.27 (0.12–0.40)	0.58 (-0.03–0.89)
MZ females	0.52 (0.45–0.58)	0.70 (0.51–0.84)
DZ females	0.28 (0.19–0.36)	0.23 (-0.10–0.53)
DZ opposite sex	0.17 (0.09–0.25)	0.16 (-0.27–0.52)

Note: LTSL = long-term sick leave; DP = disability pension.

AE, CE, and E models consecutively. It is also possible to test for a sibling interaction by including a sibling interaction parameter in the MZ- and DZ-twin covariance expressions.

Multivariate analyses. With data on multiple phenotypes, it is possible to make use of additional information in the cross-twin cross-trait correlations to examine the degree of genetic and environmental overlap between the variables (see Martin & Eaves, 1977). A common multivariate method for this aim is the Cholesky decomposition (Neale & Cardon, 1992). The triangular Cholesky decomposition is a convenient method to constrain maximum likelihood estimates of genetic and environmental covariance matrices to be positive definite. A Cholesky decomposition is first specified with all three latent sources of variance: A, C, and E. It is then possible to test the fit of different submodels using likelihood ratio χ^2 tests and AIC.

Results

The prevalence for all categories of LTSL >0 was 65.0% (48.8% for males and 76.9% for females); 18.4% of those who had LTSL in the period were on rehabilitation. Mean days of sick leave and rehabilitation during the 10-year period were 260.6 (median = 55.0). The total prevalence for all categories of DP >0 was 3.3% (2.1% for males and 4.1% for females). All of the individuals in our sample with DP had at least one episode of LTSL. Of the 253 individuals that had DP, we had information on the diagnosis for 171 persons. Of these, 51.0% had a mental disorder (ICD-9 290-320 or ICD-10 F00-F99). We did not investigate diagnoses for LTSL, as these would vary over episodes. Numbers of concordant and discordant pairs for either having or not having DP for MZ pairs were 17 and 43, respectively. For DZ pairs the corresponding numbers were 5 and 101. For either having or not having LTSL, the corresponding numbers were 582 and 375 for MZ pairs, and 795 and 710 for DZ pairs.

The polychoric twin–co-twin correlations for LTSL and DP are shown in Table 1. The DZ correlations for both males and females were approximately half the MZ correlations, indicating that additive genetic effects are important for explaining variance in the phenotype.

TABLE 2

Univariate Model Fitting Results for LTSL

Model	-2LL	*df*	*p*	AIC
1. ACE GSL	19,101.55	7,542	–	4,017.55
2. ACE CSL	19,103.09	7,543	ns	4,017.09
3. ACE NSL	19,105.22	7,546	ns	4,013.22
4. AE NSL	**19,105.22**	**7,547**	**ns**	**4,011.22**
5. AE NSL sibling interaction	19,105.09	7,546	ns	4,013.09
6. CE NSL	19,154.68	7,547	*	4,060.68
7. E NSL	19,408.33	7,548	*	4,312.33

Note: Best fitting model in bold type.
*Significant at <0.001.
LTSL = long-term sick leave; GSL = general sex limitations (allow for both qualitative and quantitative sex differences); CSL = common sex limitations (allow for quantitative sex differences); NSL = no sex limitations; ns = non-significant.

Univariate Model Fitting

For LTSL, tests of invariance showed that thresholds could not be equated across sex. We thus proceeded by fitting an ACE model allowing for qualitative and quantitative sex differences and different thresholds for males and females. The model fitting results for LTSL are shown in Table 2. We did not find any evidence of sex differences, as removing both qualitative and quantitative sex differences (Models 2 and 3) resulted in better fitting models than the full ACE model. Model 3 was therefore used for testing the significance of A and C parameters. The C parameter could be removed without significant worsening of the fit (Model 4). However, removing the A parameter, and both A and the C parameters, resulted in significant deterioration in fit (Models 6 and 7). Finally, we fit an AE model with no sex differences, but including a parameter testing for sibling interaction (Model 5). This model did have a good fit, but did not match the AIC value obtained for Model 4. The best fitting model for LTSL was therefore an AE model with no sex differences and no sibling interaction ($\Delta\chi^2 = 3.67$, $\Delta df = 5$, p = ns, AIC = 4,011.22). The additive genetic and unique environmental paths to LTSL were estimated to be 0.70 (95% CI = 0.67–0.74) and 0.71 (95% CI = 0.68–0.74), respectively. The heritability for LTSL was 0.50 (95% CI = 0.45–0.54).

For DP, we followed the same model fitting procedure as for LTSL. The model fitting results are shown in Table 3. Removing the qualitative sex differences (Model 2) resulted in a better fit than the model allowing for both types of sex differences (Model 1). Removing the quantitative sex differences (Model 3) did not result in a significantly worse fit than for Model 2. We therefore chose to proceed with Model 3 in further comparisons. As for LTSL, the best fitting model was Model 4, an AE model with no sex differences and no sibling interaction ($\Delta\chi^2 = 7.47$, $\Delta df = 5$, p = ns, AIC = -12,940.80). The additive genetic and unique environmental paths to DP were estimated to be 0.88 (95% CI = 0.80–0.93) and 0.47 (95% CI = 0.36–0.59), respectively, and the heritability was estimated to be 0.78 (95% CI = 0.65–0.87).

TABLE 3

Univariate Model Fitting Results for DP

Model	-2LL	*df*	*p*	AIC
1. ACE GSL	2,387.73	7,663	ns	-12,938.27
2. ACE CSL	2,388.28	7,664	ns	-12,939.72
3. ACE NSL	2,395.20	7,667	ns	-12,938.80
4. AE NSL	**2,395.20**	**7,668**	**ns**	**-12,940.80**
5. AE NSL sibling interaction	2,393.79	7,667	ns	-12,940.21
6. CE NSL	2,414.71	7,668	*	-12,921.29
7. E NSL	2,475.00	7,669	*	-12,863.00

Note: Best fitting model in bold type.
*Significant at <0.001.
DP = disability pension; GSL = general sex limitations (allow for both qualitative and quantitative sex differences); CSL = common sex limitations (allow for quantitative sex differences); NSL = no sex limitations; ns = non-significant.

TABLE 4

Bivariate Model Fitting Results for LTSL and DP

Model	-2LL	*df*	*p*	AIC
1. ACE	16,070.10	15,197	–	-14,323.90
2. AE	**16,070.65**	**15,200**	**ns**	**-14,329.35**
3. CE	16,125.57	15,200	*	-14,274.43
4. E	25,477.78	15,203	*	-4,928.68

Note: Best fitting model in bold type.
*Significant at <0.001.
ns = non-significant; LTSL = long-term sick leave; DP = disability pension.

Bivariate Model Fitting

In the bivariate Cholesky model, optimization problems occurred due to low prevalence of DP, which rendered fitting a full five-group model infeasible. We therefore collapsed the data into MZ and DZ twin groups without distinguishing same-sex and opposite-sex twin pairs. In order to adjust for the differences in prevalence between the sexes, we included sex as a covariate moderating the item thresholds, which is analogous to adjusting mean differences. We also reduced the number of categories from four to three for LTSL by collapsing the two middle categories (categories 1 and 2) that previously contained those with 0–5% LTSl and 5–15% LTSL, respectively, and from three to two for DP. From this data, we first fitted a full ACE model (Table 4, Model 1). We then ran AE, CE, and E submodels to test for significance of A and C parameters (Table 4).

The best fitting model was Model 2, an AE-model ($\Delta\chi^2 = 0.55$, $\Delta df = 3$, p = ns, AIC = -14,329.35). The parameter estimates for the best fitting model are shown in Figure 1. To make the parameter estimates easier to interpret, we also reparameterized the Cholesky model into a correlated factor model. Here the additive genetic and unique environmental paths to LTSL were estimated to be 0.70 (95% CI = 0.67–0.73) and 0.71 (95% CI = 0.67–0.74), respectively, which translates into a heritability estimate of 0.49. For DP, the additive genetic and unique environmental contributions were estimated to be 0.81 (95% CI = 0.69–0.96) and 0.58 (95% CI = 0.45–0.73), providing a heritability estimate of 0.66. The genetic correlation between LTSL and DP was 0.82 (95% CI = 0.80–0.90), and the correlation between the non-shared environmental factors was 0.94 (95% CI = 0.92–0.99). The phenotypic correlation was 0.86. Genes common to both phenotypes explained 55% of the phenotypic correlation, whereas the non-shared environmental factors explained 45% of the phenotypic correlation.

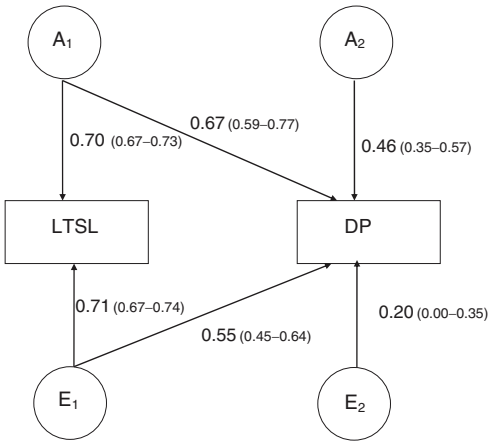


FIGURE 1

Parameter estimates for long-term sick leave (LTSL) and disability pension (DP) from the best fitting bivariate model.

Discussion

The primary question addressed in the present paper was how LTSL and DP are related to genetic and environmental etiology in a population of young adult Norwegian twins. For this purpose we used objective measures of medical benefits, and thus avoided potential biases associated with standard self-reported data (Svedberg et al., 2010).

The heritability point estimate for LTSL was 0.50 in the univariate analyses and 0.49 in the bivariate analyses. The heritability obtained in the present study is somewhat higher than recently found in a Swedish twin study, where the heritability for LTSL was 0.36 (Svedberg et al., 2012). The differences in heritability may be explained by the different measures used as well as age differences. The Swedish study used a point prevalence of LTSL, which may include more measurement errors than the method we used, namely, capturing LTSL over a period of 10 years. In addition, the Swedish sample was older (43–65 years) than the sample in the present study, and heritability may vary between different age groups.

The heritability for DP was estimated to be 0.78 in the univariate analysis and 0.66 in the bivariate analysis. Compared to previous findings, with heritability estimates ranging from 0.24 to 0.48 (Harkonmäki et al., 2008, Narusyte

et al., 2011), this is surprisingly high, as we would expect that several environmental factors, such as work conditions and health facilities, would contribute much to the liability to DP. Differences in age range may be one possible factor contributing to the differences found in heritability between the present and previous studies (birth years: 1967–1979 vs. 1925–1958, respectively). This interpretation is supported by the findings in the Swedish study (Narusyte et al., 2011), which show that the within-pair correlations decrease with age. In addition to age effects, cohort effects might also be present, as work conditions may vary for different age groups, and older employees may be more susceptible to LTSL and DP due to accumulated work-related stress.

For all analyses, the best fitting models were AE models, which suggest that the shared environmental contributions are not important for explaining sibling similarity or individual differences in LTSL and DP. In addition, none of the models that included a sibling interaction component produced a better fit to the data. Therefore, our findings give no support to a social transmission effect for these phenotypes within families. Further, no sex effects were found, suggesting that the same genetic and environmental factors influence the liability to LTSL and DP to the same extent for males and females. This is in accordance with previous studies (Svedberg et al., 2012), although indications of qualitative sex effects have been reported for DP (Narusyte et al., 2011).

Phenotypically there was a strong correlation between LTSL and DP. It is therefore not surprising that we also found a strong correlation between the variables' genetic and unique environmental risk factors ($r_G = 0.82$ and $r_E = 0.94$). These correlations suggest that the same environmental risk factors are influencing the liability to LTSL and DP, whereas the genetic factors appear to be slightly more specific to each of the phenotypes. As can be seen in the Cholesky model (Figure 1), most of the variance in LTSL and DP is explained by the common latent factors (A_1 and E_1). The common genetic factor (A_1) may reflect psychological traits such as pain tolerance, locus of control, self-efficacy, and personality traits such as neuroticism, in addition to somatic illnesses, mental disorders, and comorbidity. The genetic factor that was not shared between the phenotypes (A_2) is noteworthy, and may be important to explain why some transit from LTSL to DP, whereas others return to work. We can only speculate what this specific genetic factor reflects, but a guess is a liability to more severe mental and somatic disorders.

We were a bit surprised to find that almost all of the unique environmental variance was shared between the variables, as these factors also contain measurement error. This finding may be explained by the fact that we used data from registries, where we assume that measurement error does not contribute much to the variance. In addition, LTSL is often a prerequisite for DP. However, it should be noted that the confidence intervals for the estimate of specific E (E_2) were wide (0.00–0.35).

The notion that personality and mental disorders constitute possible risks for medical benefits, as well as for transmission from LTSL to DP, has some support, as it is found that DP due to any diagnosis can be predicted by severity of depression (Bultmann et al., 2008) and psychiatric comorbidity (Mykletun et al., 2006). Also, in a clinical cohort, personality disorders increased the risk for DP at least to the same extent as anxiety and depression (Korkeila et al., 2011). The importance of mental disorders is reflected in the diagnoses for granted DP in the study sample, as these constituted 51% of the diagnoses. The overall fraction in the Norwegian population for this age group was 51.5% in 2010 (Norwegian Labour and Welfare Service [NAV], 2010), which suggests that our sample is representative with regard to diagnoses underlying DP. Moreover, there is a reason to believe that this number is underestimated. For instance, a Norwegian study found that anxiety and depression were strong predictors for DP granted for somatic illnesses (Mykletun et al., 2006).

Limitations

A notable limitation in the present study is the low prevalence of granted DPs. As a consequence of the sparse DP data, model convergence problems occurred. The model comparisons are based on tests of differences in log likelihood, which can be hard to obtain when zero cells are present. For the bivariate models, we reduced both the number of zygosity groups and thresholds for each variable in an attempt to avert these problems. This simplification of the data could have introduced bias, and should be taken into account when interpreting the results.

A trend in the data of higher correlations in same-sex twins than in opposite-sex DZ twins suggests that there may be qualitative sex-specific genetic effects that we did not have power to detect. Undetected sex effects can inflate the heritability estimates. We can therefore not rule out the possibility that the estimates may have looked different had we had a larger sample.

For these analyses, it was necessary to carry out substantial pre-processing of the data for each of the phenotypes. LTSL and DP data covered a 10-year time span and were aggregated to construct the phenotypic variables. This resulted in having to collapse across different time periods, as well as possibly heterogeneous trajectories, particularly for DP. Such complex longitudinal data leaves open the possibility of carrying out additional analyses that examine the time-dependent nature of the data, which may provide a more detailed and possibly different picture of the etiologies underlying the phenotypes.

In the present study we found differences in heritability between the univariate and bivariate analyses for LTSL and DP. However, this was not unexpected, and may be due to the differences in the number of thresholds and collapsing

of zygosity groups. Conducting bivariate twin analyses may help stabilize the estimates of low-prevalent traits as we can rely on cross-twin cross-trait correlations as well as twin correlations.

Expressed macro-level traits, such as the two investigated here, are the result of a complicated interplay between genes and environments, for instance in form of gene–environment correlation (r_{GE}) and gene–environment interaction (G × E; Jaffee and Price, 2007). For most complex traits, we cannot yet claim to have an in-depth understanding of the causal paths leading from a genetic potential to the resulting trait. It is therefore possible that the estimates obtained would have looked somewhat different had we been able to test for these effects.

We used a sample of young adult Norwegian twins. The results may thus not be representative for other populations and age cohorts. As noted when comparing our results to the Finnish and Swedish studies of DP, the genetic factors involved may vary as a function of age. Another potential limitation is that DP may be correlated with age. In our sample the polychoric correlation between age and DP was -0.13. Although this is a low correlation, it may have inflated twin correlations because co-twins have the same age. Thus, we would expect an inflated estimate of shared environment (C). However, as we found no evidence of C, such an inflation cannot have been important.

In summary, we found evidence indicating substantial heritability for both LTSL and DP in our data, and no evidence of shared environmental or social transmission effects. Our main finding was that the genetic and environmental risk factors for LTSL and DP overlapped to a strong degree, with the exception of a genetic factor that distinguishes LTSL from DP. Given that DP grants based on mental disorders are quite prevalent in this age group, future research should investigate association between these disorders and LTSL and DP.

Acknowledgments

The work was supported by a grant from the Sickness Absence Research Programme at the Norwegian Research Council. Data on zygosity on the twins used in this study was obtained from the Norwegian Twin Registry and the Norwegian Institute of Public Health. The work was also in part supported by NIH grant MH-068643. We are very grateful to the twins for their participation.

References

Akaike, H. (1987). Factor analysis and AIC. *Psychometrica, 52*, 317–332.

Akselsen, A., Lien, S., & Siverstøl, Ø. (2007). *FD-trygd. List of variables.* Oslo, Norway: Statistics Norway.

Battie, M. C., Videman, T., Levalahti, E., Gill, K., & Kaprio, J. (2007). Heritability of low back pain and the role of disc degeneration. *Pain*, *131*, 272–280.

Besseling, J. J. M., Rijkenberg, A. M., Andriessen, S., & de Vos, E. L. (2008). Increasing use of social benefits by young people with chronic illness or disability in the Netherlands. *Rehabilitation, 47*, 366–371.

Boker, M. S., Neale, M. C., Maes, H., Wilde, M., Spiegel, M., Brick, T., . . . Fox, J. (2011). OpenMx: An open source extended structural equation modeling framework. *Psychometrica*, *76*, 306–317.

Bultmann, U., Christensen, K. B., Burr, H., Lund, T., & Rugulies, R. (2008). Severe depressive symptoms as predictor of disability pension: A 10-year follow-up study in Denmark. *European Journal of Public Health*, *18*, 232–234.

Eaves, L. (1976). A model for sibling effects in man. *Heredity*, *36*, 205–214.

Falconer, D. S. (1965). Inheritance of liability to certain diseases estimated from incidence among relatives. *Annual of Human Genetics*, *29*, 51–76.

Gjesdal, S., & Bratberg, E. (2003). Diagnosis and duration of sickness absence as predictors for disability pension: Results from a three-year multi-register based and prospective study. *Scandinavian Journal of Public Health*, *31*, 246–254.

Gjesdal, S., Haug, K., & Ringdal, P. R. (2005). The risk of disability pension among young persons on long-term sick leave. *Tidsskrift for Den Norske Lægeforeningen*, *125*, 1801–1805.

Harkonmäki, K., Silventoinen, K., Levälahti, E., Pitkäniemi, J., Huunan-Seppälä, A., Klaukka, T., . . . Kaprio, J. (2008). The genetic liability to disability retirement: A 30-year follow-up study of 24,000 Finnish twins. *PloS ONE*, *3*, e3402.

Harris, J. R., Magnus, P., & Tambs, K. (2006). The Norwegian Institute of Public Health Twin Program of Research: An update. *Twin Research and Human Genetics*, *9*, 858–864.

Ihlebaek, C., Brage, S., & Eriksen, H. R. (2007). Health complaints and sickness absence in Norway, 1996–2003. *Occupational Medicine*, *57*, 43–49.

Jaffee, S. R., & Price, T. S. (2007). Gene-environment correlations: A review of the evidence and implications for prevention of mental illness. *Molecular Psychiatry*, *12*, 432–442.

Jinks, J. L., & Fulker, D. W. (1970). Comparison of biometrical genetical, MAVA, and classical approaches to analysis of human behavior. *Psychological Bulletin*, *73*, 311–349.

Kendler, K. S., & Prescott, C. A. (2006). *Genes, environment, and psychopathology: Understanding the causes of psychiatric and substance use disorders.* New York, NY: Guilford Press.

Knudsen, A. K., Overland, S., Hotopf, M., & Mykletun, A. (2012). Lost working years due to mental disorders: An analysis of the Norwegian Disability Pension Registry. *Plos One*, *7*, e42567.

Korkeila, J., Oksanen, T., Virtanen, M., Salo, P., Nabi, H., Pentti, J., . . . Kivimaki, M. (2011). Early retirement from work among employees with a diagnosis of personality disorder compared to anxiety and depressive disorders. *European Psychiatry*, *26*, 18–22.

Magnus, P., Berg, K., & Nance, W. E. (1983). Predicting zygosity in Norwegian twin pairs born 1915–1960. *Clinical Genetics*, *24*, 103–112.

Martin, N. G., & Eaves, L. J. (1977). The genetical analysis of covariance structure. *Heredity*, *38*, 79–95.

Moncrieff, J., & Pomerleau, J. (2000). Trends in sickness benefits in Great Britain and the contribution of mental disorders. *Journal of Public Health Medicine*, *22*, 59–67.

Mykletun, A., Overland, S., Dahl, A. A., Krokstad, S., Bjerkeset, O., Glozier, N., & Aaro, L. E. (2006). A population-based cohort study of the effect of common mental disorders on disability pension awards. *American Journal of Psychiatry*, *163*, 1412–1418.

Narusyte, J., Ropponen, A., Silventoinen, K., Alexanderson, K., Kaprio, J., Samuelsson, A., & Svedberg, P. (2011). Genetic liability to disability pension in women and men: A prospective population-based twin study. *PloS ONE*, *6*, e23143.

Neale, M. C. (2003). A finite mixture distribution model for data collected from twins. *Twin Research*, *6*, 235–239.

Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families*. Dordrecht, the Netherlands: Kluwer.

Neale, M. C., & Maes, H. H. (2000). *Methodology for genetic studies of twins and families*. Dordrecht, the Netherlands: Kluwer.

Norwegian Labour and Welfare Service (NAV). (2010). *Disability pension recipients — Diagnosis, age and sex*. Retrieved from http://www.nav.no

Norwegian Official Reports (NOU). (2000). *Sickness absence and disability pensioning — A labour market for all*. Oslo, Norway: NOU.

Organisation for Economic Co-operation and Development (OECD). (2003). *Transforming disability into ability. Policies to promote work and income security for disabled people*. Paris, France: OECD.

Ose, S. O. (2010). *Knowledge about sickness absence: New Norwegian contributions*. Trondheim, Norway: SINTEF.

R Development Core Team. (2005). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing.

Soderberg, E., & Alexanderson, K. (2003). Sickness certification practices of physicians: A review of the litterature. *Scandinavian Journal of Public Health*, *31*, 460–474.

Svedberg, P., Ropponen, A., Alexanderson, K., Lichtenstein, P., & Narusyte, J. (2012). Genetic susceptibility to sickness absence is similar among women and men: Findings from a Swedish twin cohort. *Twin Research and Human Genetics*, *15*, 642–648.

Svedberg, P., Ropponen, A., Lichtenstein, P., & Alexanderson, K. (2010). Are self-report of disability pension and long-term sickness absence accurate? Comparisons of self-reported interview data with national register data in a Swedish twin cohort. *BMC Public Health*, *10*, 763.

Tallis, G. M. (1962). The maximum likelihood estimation of correlation from contingency tables. *Biometrics*, *18*, 342–353.

Tambs, K., Ronning, T., Prescott, C. A., Kendler, K. S., Reichborn-Kjennerud, T., Torgersen, S., & Harris, J. R. (2009). The Norwegian Institute of Public Health Twin Study of Mental Health: Examining recruitment and attrition bias. *Twin Research and Human Genetics*, *12*, 158–68.

PAPER 3

Gjerde, L. C., Røysamb, E., Czajkowski, N., Knudsen, G. P., Østby, K., Tambs, K., Kendler, K. S., Reichborn-Kjennerud, T., & Ørstavik, R. E. (in press). Personality disorders and long-term sick leave: a population-based study of young adult Norwegian twins. *Twin Research and Human Genetics*.

PERSONALITY DISORDERS AND LONG-TERM SICK LEAVE: A POPULATION-BASED STUDY OF YOUNG ADULT NORWEGIAN TWINS

L. C. Gjerde
E. Røysamb
N. Czajkowski
G. P. Knudsen
K. Østby
K. Tambs
K. S. Kendler
T. Reichborn-Kjennerud
R. E. Ørstavik

From the Department of Mental Health, Norwegian Institute of Public Health (L.C. Gjerde, N. Czajkowski, E. Røysamb, K. Tambs, K. Østby, G.P. Knudsen, T. Reichborn-Kjennerud and R.E. Ørstavik), the Institute of Psychiatry, University of Oslo, Norway (T. Reichborn-Kjennerud), Department of Psychology, University of Oslo, Norway (E. Røysamb, N. Czajkowski), and Virginia Institute for Psychiatric and Behavioral Genetics and Departments of Psychiatry and Human Genetics and Medical College of Virginia/Virginia Commonwealth University, Richmond, VA. USA (K. S. Kendler).

Running title: Personality disorders and long-term sick leave

Corresponding address:

Line C. Gjerde, Norwegian Institute of Public Health, Box 4404, Nydalen N-0403 Oslo, Norway. Phone: +47 45 44 33 03, fax: +47 21 07 82 60 e-mail: line.gjerde@fhi.no

ABSTRACT

Personality disorders (PDs) reduce global functioning, are associated with high levels of work disability, and are thus also likely to influence long-term sick leave (LTSL). Previous research has indicated significant genetic influence on both DSM-IV PDs and LTSL. To what degree genes contributing to PDs also influence LTSL has not been investigated. The aims for the current study were to investigate which PDs were significantly associated with LTSL, to what extent the genetic contributions to these PDs account for the heritability of LTSL, and to explore the hypothesis of a causal association between PDs and LTSL. The sample consisted of 2,771 young, adult Norwegian twins, born 1967-1979. PDs were assessed using the Structured Interview for DSM-IV Personality (SIDP-IV). The age range at interview was 20-32. The data were subsequently linked to public records of LTSL (sick leave >16 days) up to 11 years later. The odds ratio for being in the highest LTSL category (>15% sick leave) when fulfilling the DSM-IV criteria for any PD diagnosis was 2.6 (1.8-3.8, 95% CI). Dimensional representations of schizotypal, paranoid and borderline PD were independently and significantly associated with LTSL. The heritability of LTSL was 0.50. Genetic factors shared with the PDs accounted for 20% of this. The association between PDs and LTSL was due to shared genetic and not environmental influences, and was mainly explained by one common genetic factor. The hypothesis of a causal association was not supported, indicating that the association is explained by overlapping genetic liability between PDs and LTSL.

INTRODUCTION

High levels of sick leave cause concern in many developed countries, as this is a burden both for affected individuals and workplaces, and for the economy in general (Moncrieff & Pomerleau, 2000; OECD, 2010). Sick leave benefits are granted for disease or injury that results in reduced work capacity (Soderberg & Alexanderson, 2003). Sick leave constitutes a complex phenomenon with many potential risk factors (Dekkers-Sanchez et al., 2008). Definitions and processes of certification vary across countries (Henderson et al., 2011) and this might partly explain the lack of an international research standard for defining sick leave, and for separating short- from long-term sick leave. The focus in this study is on long-term sick leave, hereafter referred to as LTSL. Research on LTSL is important, as individuals who have had one or more episodes of LTSL have increased risk for disability pensioning (Gjesdal et al., 2005; Hultin et al., 2012).

LTSL du to mental disorders has increased in western countries in the last two decades (Hensing et al., 2006; Vaez et al., 2007). Anxiety and depression are important risk factors for LTSL (Knudsen et al., 2013). Mental disorders most often emerge in adolescence and early adulthood (Kessler et al., 2005) and may therefore be particularly detrimental to education and subsequent employment (Suvisaari et al., 2009). Despite the increased focus on mental disorders and sick leave, few studies have investigated effects of less common mental disorders, such as personality disorders (PDs) in young adults.

The DSM-IV Axis II system includes 10 PDs, ordered into three clusters (APA, 1994). PDs are characterized by persistent, maladaptive patterns of inner experience and behavior that leads to distress and impairment (APA, 1994). The worldwide prevalence of PDs has recently been estimated to 6.1% (Huang et al., 2009). There is extensive comorbidity among the different PDs (Coid et al., 2006; Marinangeli et al., 2000), indicating that multiple PD diagnoses are most common (Marinangeli et al., 2000). Although treated as categorical

diagnoses in DSM-IV, strong empirical support exists to conceptualize PDs dimensionally (Livesley & Jang, 2000; Trull & Durrett, 2005; Widiger & Mullins-Sweatt, 2009). Many have also argued that there are strong links between PDs and the general personality structure, where PDs may represent extremities of normal personality (R. R. McCrae et al., 2005; Widiger & Trull, 2007).

Much is known about the underlying genetic and environmental structure of PDs (Kendler et al., 2008; Kendler et al., 2011; Roysamb et al., 2011), but less about the consequences of PDs, particularly for work participation. Both PDs and extreme scores on normal personality traits decrease global functioning (R. R. McCrae et al., 2005; Skodol et al., 2007), and GAF scores have been found to decrease with increasing number of PD criteria met (Nakao et al., 1992). Extreme scores on personality traits are also associated with impaired work functioning (Michon et al., 2008) and short- and long-term sick leave (Stormer & Fahr, 2013; Vlasveld et al., 2012). We are not aware of studies that have investigated the association between PDs and sick leave per se, but PDs have been found to be associated with problems maintaining job positions (Noren et al., 2007). Further, borderline, dependent, schizoid and schizotypal PD are found to be significantly associated with disability pensioning (Knudsen et al., 2012; Østby et al., submitted).

Both PDs and LTSL are influenced by genetic as well as environmental factors. The heritability for dimensional representations of DSM-IV PDs varies between 0.21 and 0.38 (Kendler et al., 2006; Reichborn-Kjennerud et al., 2007; Torgersen et al., 2008), and between 0.36 and 0.49 for LTSL defined as sick leave extending 15-16 days (Gjerde et al., 2013; Svedberg et al., 2012). As no specific genes are expected for LTSL per se, it is important to investigate to what extent genetic contributions to mental disorders, such as PDs, can account for the heritability.

If an association exists between specific PDs and LTSL, it is necessary to establish the nature of this association. A natural next step after investigating heritability is to investigate whether these phenotypes share genetic and/or environmental contributions. This has, to our knowledge, not yet been investigated. By clarifying this, the question of causal pathways can also be illuminated. Although multivariate Cholesky models are not in themselves designed to establish causal pathways, some inferences can be made. For phenotypes that are influenced by both genetic and environmental factors, as is the case for both PDs and LTSL (Gjerde et al., 2013; Kendler et al., 2006; Reichborn-Kjennerud et al., 2007; Svedberg et al., 2012; Torgersen et al., 2008), a pure genetic correlation would not indicate causality, but rather that the association is mediated through genetic factors shared between the phenotypes (De Moor et al., 2008; Kendler et al., 1993).

The aims for the present study were: 1) to investigate whether there is an association between DSM-IV PDs and LTSL defined as sick leave >16 days; 2) to identify which PDs are most important for the association; 3) to investigate to what extent the heritability of LTSL can be accounted for by genetic contributions to PDs, and; 4) to explore whether the association between PDs and LTSL is causal or due to other factors.

MATERIAL AND METHODS

SAMPLE

Data for the current analyses originate from the Norwegian Institute of Public Health Twin Panel (NIPHTP). The twins were identified through the national Medical Birth Registry, established January 1, 1967. Our sample consisted of those who had participated in a psychiatric interview study, conducted between June 1999 and May 2004 (90% within the end of 2002). Participants were recruited from 3,153 complete twin pairs who had given consent to be contacted again after a previous questionnaire study, and 68 twin pairs drawn directly

from the NIPHTP. The response rate was 43.5% (2,801 out of 6,442), and 2,794 of the interview responses were valid. Non-participants consisted of 0.8% pairs not willing or able to participate, 16.8% pairs in which only one twin agreed to participate, and 38.9% pairs in which none responded after reminders. In 22 pairs where both twins initially agreed to be interviewed, the co-twin later declined. The high rate of attrition from the questionnaire studies to the interview study has been found not to affect twin analyses of mental health related variables (Tambs et al., 2009).

The interviews were mainly conducted by psychology students late in their training and psychiatric nurses who received a standardized training program by teachers certified by the WHO. Members of a pair were assessed by different interviewers blind to the information obtained from the co-twin. The majority of interviews were conducted face-to-face, and 231 were interviewed over the phone.

By using the unique national identification numbers issued to all Norwegians at birth, data were in 2011 linked to the historical-event database (FD-Trygd). This database contains information regarding all social security benefits, including e.g., sickness benefits, social assistance, rehabilitation allowance, disability pension and unemployment benefits (Akselsen et al., 2007). As the register data at Statistics Norway are updated annually, we have obtained a detailed, longitudinal dataset on the twins, including annual information on the variables listed above from 1998 to 2008. The number of individuals with valid interview data after linkage was 2,771 (mean age in 1998: 25.6 years), as 23 declined to participate. For 4 of the 2,771 we lack information on zygosity. The sample for the twin modelling analyses was therefore 2,767 including 1,365 complete pairs, comprising 219 monozygotic (MZ) male pairs, 117 dizygotic (DZ) male pairs, 436 MZ female pairs, 257 DZ female pairs, 336 DZ opposite sex pairs and 37 single responders.

Zygosity was initially determined using questionnaire items previously shown to classify correctly more than 97% of the twin pairs (Magnus et al., 1983), followed by DNA analyses on a subgroup of the sample. The discrepancy between classification based on the questionnaire and DNA markers implied an expected misclassification rate of <1% for the whole sample, which is unlikely to bias our results (Neale, 2003).

For the interview study, approval was received from the Regional Ethical Committee and the Norwegian Data Inspectorate, and written informed consent was obtained from the participants after complete description of the study. The linkage of data from NIPHTP with registries at Statistics Norway was approved by the Regional Ethical Committee.

MEASURES

In Norway, the first 16 days of sick leave is paid for by the employers, and thereafter mandatorily covered by the Norwegian Insurance Scheme (NIS) for up to 52 weeks (Gjesdal & Bratberg, 2003). We defined LTSL as sickness absence of >16 days, the minimum sick leave period recorded in our dataset. After 52 weeks of sick leave, an individual who is still unable to work can be granted medical and/or vocational rehabilitation benefits in order to undergo treatment or training aimed at regaining work ability (NOU, Norwegian Official Reports 2000:27). We included periods of receiving rehabilitation benefits in the LTSL variable, as this reflects a continuation of LTSL. The total number of sick days, rehabilitation and working days in the 11 year long follow up period were summed; either up to the time of granted disability pension (N=76), death (N=12) or by the end of 2008. The LTSL variable was then constructed as a ratio (0-100%) between the cumulative number of sick days and rehabilitation days over potential working days (Gjerde et al., 2013). The LTSL proportion variable was positively skewed (skewness: 3.0, kurtosis: 9.0), and was thus further divided into four categories; “0” = no registered sick leave in the period (N=2,646), “1” = up to 5%

LTSL in the period (N=2,249), “2” = 5-15% LTSL in the period (N=1,411), and “3” = >15% LTSL in the period (N=1,251). This variable had acceptable skewness and kurtosis values (0.4 and -1.1, respectively) and correlated 0.86 with the sum of the number of sick days in the observation period. A multiple threshold test confirmed that the LTSL categories reflect differences of severity on a normally distributed liability continuum. Only subjects eligible for sickness allowance during the period were included in the analyses; 153 twins were censored out, either due to no work in the period (N=143) or for being granted disability pension before 2000 (N=10).

PDs were assessed by a Norwegian version of the SIDP-IV (Pfohl & Zimmerman, 1995), a comprehensive semi-structured diagnostic interview for the assessment of all DSM-IV Axis II diagnoses. The instrument includes non-pejorative questions organized into topical sections to produce a natural flow in the interview. The questions address behaviors, cognitions and feelings that have been predominant for most of the past 5 years, and thus are considered to be representative for the individual’s long-term personality functioning. This 5 year assumption is supported by empirical evidence of high stability of normal personality traits during adulthood (R.R McCrae & Costa, 1990). Each DSM-IV criterion is scored as 0 = ”absent”, 1 = “subtreshold”, 2 = “present” or 3 = “strongly present”.

For the bivariate logistic regression analysis, we constructed a dichotomous variable defined as having at least one full categorical DSM-IV PD diagnosis (a score of ≥2 on at least 3 to 5 SIDP-IV criteria) (APA, 1994).

In the rest of the analyses of the SIDP-IV data, we used a dimensional approach by constructing the PDs as ordinal variables. The number of criteria scored ≥1 was summed, assuming that the liability for each trait is continuous and normally distributed. Due to low prevalence of full PDs, the PD variables were truncated by collapsing the upper criteria counts into three to five categories to avoid empty cells in the twin analyses. This approach has been

used in previous publications on the same sample (Gjerde et al., 2012; Kendler et al., 2006; Kendler et al., 2007; Reichborn-Kjennerud et al., 2007; Torgersen et al., 2008). The PD variables have been tested and approved with multiple threshold tests used to examine whether they can be regarded as differences of severity on a normally distributed continuum of liability (see e.g. Kendler et al., 2006). Thus, for convenience we refer to PDs, but are in fact assessing dimensional representations of PDs.

Inter-rater reliability was assessed by two raters scoring 70 audio-taped interviews. Intra-class correlations for the number of endorsed PD criteria at the subthreshold level ranged from +0.81 to +0.96.

STATISTICAL ANALYSES

Regression analyses

We first conducted a simple logistic regression analysis between the LTSL variable (dichotomized into above/below15% sick leave days) and any categorical DSM-IV PD diagnosis, in order to demonstrate the crude association between PDs and LTSL.

To explore which dimensional representations of PDs were associated with LTSL, we conducted ordinal logistic regression analyses, first separately and then in a multivariate model including the PDs that were significantly associated with LTSL. As the PDs consists of sum scores of criteria ≥1 truncated into 3 to 5 groups, the resulting odds ratios (OR) are not directly comparable between the PDs. We adjusted for sex in all the regression analyses, as prevalence rates for the PDs varies across sex. We corrected for dependency between twin pairs using generalized estimating equations (GEE) (Dobson, 2002). The significance level was set to 0.05. All PDs have previously been found to correlate weakly to moderately (0.13-0.58) (Roysamb et al., 2011), indicating that multicollinearity was not an issue.

Twin model fitting

As our data are ordinal, we use a liability-threshold model (Falconer, 1965) to estimate the genetic and environmental contributions to twin resemblance on the variables. We assume that ordered categories are indicators of an unobserved, normally distributed liability that can be estimated as thresholds discriminating between the categories.

In the classical twin design (Jinks & Fulker, 1970; Martin & Eaves, 1977), individual differences in liability are assumed to arise from additive genetic (A), shared environmental (C), and non-shared environmental (E) sources. As MZ twins share all, and DZ twins share on average half of their segregating genes, A would tend to make MZ twins correlate twice as high as DZ twins. C is defined as environmental factors contributing to similarity between twins, and is further assumed to have an equal effect on MZ and DZ twins. E is per definition not shared between twins in a pair, and hence does not contribute to twin similarity. E also contains measurement error. The influence of these factors on the variables can be estimated using structural equation modelling (SEM; Neale & Maes, 2000). The liability-threshold models were fitted on raw data in OpenMx (Boker et al., 2011), which has the advantage of including single responders, and thus maximizing power. The difference in -2 times log likelihood (Δ-2LL) is asymptotically χ^2 distributed, allowing testing for significant deterioration in χ^2 for nested submodels. If the difference in χ^2 is non-significant, the simpler model is preferred over the more highly parameterized and complex model. In addition, as an index of parsimony, Akaike Information Criterion (AIC), calculated as χ^2 - 2df (Akaike, 1987) was used to select the best fitting model. Preferred models are those with the lowest AIC-value.

For the current study, multiple phenotypes were analysed simultaneously. Multivariate analyses can be advantageous, compared to univariate analyses, as having multiple phenotypes makes it possible to use the additional information inherent in cross-twin cross-

trait correlations (Martin & Eaves, 1977). A common multivariate method is the triangular Cholesky decomposition (Neale & Cardon, 1992), which is a convenient method for constraining maximum likelihood estimates of genetic and environmental covariance matrices to be positive definite. We first fitted a full ACE multivariate Cholesky model to the data, allowing for quantitative (scalar) sex differences. Quantitative sex differences involve the same genetic and environmental effects for males and females, but in different quantity for the sexes. We therefore constrained the A and C correlations to be equal for males and females based on the strategy suggested by Neale et al. (Neale et al., 2006). We tested for quantitative sex differences (Common sex limitation model [CSL]) by allowing the A, C and E parameter effects to differ across male and female twins and then compared the fit of this model with a model constraining the parameters to be equal across sex (No sex limitation model [NSL]). We could not test for qualitative sex differences, which involve different genetic and/or environmental effects for males and females, as this is problematic in a multivariate Cholesky model (Neale et al., 2006). After testing for sex differences, we ran submodels to test for significance of the A and C parameters by fixing selected parameters to be 0 in an AE-, CE- and E model, consecutively.

RESULTS

The prevalence of having had at least one episode of LTSL in the 11 year long follow-up period was 63.9% (45.9% for males and 74.4% for females). The number of days of sick leave (from sick leave periods >16 days) and rehabilitation in the period ranged from 0 to 3,717 days (0-3,673 for males), although 95% of the sample was within a range of 0-1,300. Median days were 53 (0 for males and 117 for females). The mean number of sick leave periods >16 days was 1.9. By the end of the observation period (2008) 48.5% had achieved education at a tertiary level (undergraduate or postgraduate) which was slightly higher than

the general population in the same age group (SSB, 2013), 65% had children, and 44.4% were married. 99.9% of the sample was registered as working at least one time during the observation period. After separating out those without work, work days ranged from 44 to 4,015 days (median: 2,841 days). The prevalence of any categorical PD diagnosis was 5.1%. The mean number of subthreshold PD-criteria varied between 0.4 for schizoid PD (SPD) and 1.9 for obsessive-compulsive PD (OCPD).

REGRESSION ANALYSES

The OR for being in the highest LTSL group (>15% of working days) when fulfilling the criteria for at least one categorical DSM-IV PD diagnosis was 2.6 (1.8-3.8, 95% CI).

The results from the GEE ordinal logistic regression analyses are shown in Table 1.

Insert Table 1 about here

When testing each dimensional PD against LTSL and adjusting for sex, all PDs were positively and significantly associated with LTSL with the exception of: antisocial PD (APD), narcissistic PD (NPD) and schizoid PD (SPD). From the multiple GEE ordinal logistic regression analysis where we adjusted for sex and all of the significantly associated dimensional PDs, three PDs were uniquely and positively related to LTSL: schizotypal PD (STPD), borderline PD (BPD) and paranoid PD (PPD).

TWIN MODEL FITTING

The three PDs significantly associated with LTSL were included in a tetravariate Cholesky model along with LTSL. STPD was placed first in the model, as this had the strongest association with LTSL in the regression analyses. PPD was placed second, as this is also a

Cluster A PD, whereas BPD, from Cluster B, was placed third. The variables had different prevalence across sex. We therefore used separate thresholds for males and females. The results for the twin model fitting are shown in Table 2.

Insert Table 2 about here

Model 6, an AE-model with no sex differences, fitted significantly poorer than Model 1 to the data on a p= 0.05 level ($\Delta\chi^2 = 38.78$, $\Delta df = 24$, $p = 0.03$, AIC = 2,333.72). However, as the AIC was lowest for Model 6, we selected this as best fitting. The parameter estimates for the best fitting model are shown in Figure 1. The genetic and environmental correlations between the variables are shown in Table 3. The phenotypic correlations between STPD, PPD, BPD and LTSL were +0.19 (0.14-0.24, 95% CIs), +0.17 (0.13-0.22, 95% CIs), and +0.13 (0.08-0.18, 95% CIs), respectively. The heritabilities for STPD, PPD, BPD and LTSL were 0.26 (0.15-0.36, 95% CIs), 0.22 (0.15-0.30, 95% CIs), 0.32 (0.23-0.41, 95% CIS) and 0.50 (0.46-0.55, 95% CIs), respectively.

Insert Table 3 about here

Ninety percent of the phenotypic variance in LTSL was not related to the PDs. The remaining 10% was almost entirely due to the influence of shared genetic variance, as the unique environmental variance shared between the PDs and LTSL was less than 1%. Thus, 20% ($0.28^2+0.13^2/0.50$) of the heritability of LTSL was explained by the genetic variance shared with the PDs.

Insert Figure 1 about here

DISCUSSION

We studied a population-based sample of 2,771 young adult Norwegian twins, born 1967-1979, for which we had an 11 year follow-up period (1998-2008) covering sick leave and rehabilitation days. Our first aim was to investigate whether there was a significant association between PDs and LTSL. We found that those in the highest LTSL category had an OR of 2.6 for having at least one categorical PD diagnosis when compared to those in the lowest LTSL category. This finding is in accordance with a previous study that found an OR of 2.76 between disability pensioning and any probable PD diagnosis and (Knudsen et al., 2012). For our second aim, we found that most of the PDs were significantly associated with LTSL. When adjusting for the other significant PDs, only three PDs remained significantly associated with LTSL, namely STPD, PPD and BPD, which may reflect the extensive comorbidity between PDs (Coid et al., 2006; Lenzenweger et al., 2007; Marinangeli et al., 2000). Thus, the general PD tendency that increases risk for LTSL may be mediated through traits associated with these three disorders. A previous study on the same sample found that SPD, BPD and dependent PD (DEPD) were significantly associated with disability pensioning after adjusting for other PDs, socioeconomic status and sex (Østby et al., submitted). These findings are similar to ours, as SPD is often associated with STPD (Lenzenweger et al., 2007), but diverge with regard to DEPD and PPD. The different results may be explained by the different outcomes – sick leave versus disability pensioning, and the different designs.

Two of the PDs found to be significantly associated with LTSL, STPD and PPD, are placed in the DSM-IV Axis II Cluster A group, characterized by odd and eccentric traits. BPD is placed in the Cluster B group, characterized by dramatic, emotional and erratic traits (APA, 1994). STPD is associated with discomfort in close relationships, and preference for spending

time alone (APA, 1994). This could complicate work force participation. Individuals with STPD may also be suspicious and have excessive social anxiety (APA, 1994), which makes it difficult to interact with colleagues and thus may increase the risk for LTSL. The most important characteristics of individuals with PPD are pervasive distrust and suspiciousness of other people (APA, 1994). These characteristics, along with a grudging attitude towards others and vigilance for possible attacks, will make it hard to function in a work environment. BPD is characterized by instability of interpersonal relationships, self-image and affects (APA, 1994), and individuals suffering from BPD often experience high emotional distress along with varying degrees of mental and physical disability (Grant et al., 2008; Holm & Severinsson, 2008). Many of the criteria for BPD make it difficult to maintain and thrive in a job. Symptoms such as strong reactivity to interpersonal stresses, dysphoric mood, self-harm, and suicidal thoughts are all possible causes for frequent or long episodes of sick leave.

Our third aim was to estimate to what extent the genetic contributions to the selected PDs could account for the heritability of LTSL. We found that the genetic contributions to STPD, PPD and BPD could account for a modest amount (20%) of the heritability of LTSL. The association was mainly due to one genetic factor shared in common for PDs and LTSL, as the second factor was not statistically significant. This finding is in accordance with a previous study that showed substantial genetic overlap between DSM-IV PDs (Kendler et al., 2008). The best fitting twin model according to AIC was an AE model with no sex differences, and hence we did not find evidence for shared environmental effects or genetic and environmental factors influencing PDs and LTSL to different degrees for males and females.

For the fourth aim, we explored the hypothesis of a causal pathway between PDs and LTSL. As PDs and LTSL were found to be influenced by both genetic and environmental factors (Figure 1), there should be both a genetic and an environmental correlation between at

least one of the PDs and LTSL for us to argue that the association could be causal (De Moor et al., 2008; Ligthart & Boomsma, 2012). We found significant genetic correlations between all three PDs and LTSL, but small and mostly non-significant environmental correlations (Table 3). Thus, our results do not support a causal association. It could be that if most of the E effects were due to measurement error, and these could be separated out, we would expect higher and maybe significant E cross-loadings. However, there is not reason to assume that most of the E effects are measurement errors, as previous studies have shown that even after correcting for measurement error, there are substantial E effects for PDs (Gjerde et al., 2012; Kendler et al., 2007; Torgersen et al., 2012). We do not know of any studies that have corrected for measurement error on LTSL, but as this is a population-based registry measure, we expect such errors to be of limited importance. To reach a more informed conclusion on the issue of causality a more formal model testing approach should be used with a larger sample (Neale & Kendler, 1995).

Despite the absence of evidence for a causal association, early detection and treatment of STPD, PPD and BPD is important, as these have previously been found to be the most impairing types of PDs (Nakao et al., 1992). The finding that PDs do not seem to be causally related to LTSL could be due to limited statistical power and should therefore be interpreted with caution.

LIMITATIONS

Due to the low prevalence of categorical PDs in the current sample, we used dimensional representations of PDs to be able to carry out the twin modeling analyses. There is, however, strong empirical support for conceptualizing PDs as dimensions (Widiger & Mullins-Sweatt, 2009).

As PDs were measured between 1999 and 2004, although 90% within the end of 2002, whereas LTSL was measured between 1998 and 2008, it could be argued that we should have censored out LTSL before 2004. However, as PDs have an onset in adolescence or early adulthood (APA, 2000), and are measured as "during the last 5 years", we feel confident that PDs preceded LTSL in the observation period.

We could not test for qualitative sex differences due to limitations posed by the multivariate Cholesky model (Neale et al., 2006). Further, the finding of no quantitative sex differences or shared environmental effects could be due to limited statistical power. More studies with larger sample sizes are needed to conclude on whether sex differences or shared environmental effects are important to explain individual differences in PDs and LTSL.

The sample used in the present study consisted of young adult Norwegian twins, and it is possible that the results are not representative for other age- or ethnic groups.

CONCLUSION

The aim of the present study was to clarify the largely unexplored association between PDs and LTSL among young adults. STPD, PPD and BPD were significantly associated with LTSL after adjusting for sex and comorbidity of other significant PD traits. Genetic contributions to these PDs accounted for 20% of the heritability of LTSL. The association between the PDs and LTSL was mainly due to one shared genetic factor, rendering a causal relationship between PDs and LTSL unlikely.

ACKNOWLEDGEMENTS

The work was supported by a grant from The Sickness Absence Research Programme at The Norwegian Research Council. The collection of twin data was also in part supported by previous grants from The Norwegian Research Council, The Norwegian Foundation for Health and Rehabilitation, and The Norwegian Council for Mental Health. We are very grateful to the twins for their participation.

REFERENCES

Akaike, H. (1987). Factor analysis and AIC. *Psychometrica, 52*, 317-332.

Akselsen, A., Lien, S., & Siverstøl, Ø. (2007). FD-trygd. List of variables. Oslo: Statistics Norway.

APA. (1994). *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.). Washington: American Psychiatric Association.

APA. (2000). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*. Washington, DC: American Psychiatric Association.

Boker, M.S., Neale, M. C., Maes, H., Wilde, M., Spiegel, M., Brick, T., Spies, J. , Estabrook, R., Kenny, S., Bates, T. , Mehta, P., & Fox, J. (2011). OpenMx: An open source extended structural equation modeling framework. *Psychometrica, 76*(2), 306-317.

Coid, J., Yang, M., Tyrer, P., Roberts, A., & Ullrich, S. (2006). Prevalence and correlates of personality disorder in Great Britain. *British Journal of Psychiatry, 188*, 423-431.

De Moor, M. H. M., Boomsma, D. I., Stubbe, J. H., Willemsen, G., & de Geus, E. J. C. (2008). Testing causality in the association between regular exercise and symptoms of anxiety and depression. *Archives of General Psychiatry, 65*(8), 897-905.

Dekkers-Sanchez, P. M., Hoving, J. L., Sluiter, J. K., & Frings-Dresen, M. H. W. (2008). Factors associated with long-term sick leave in sick-listed employees: a systematic review. [Review]. *Occupational and Environmental Medicine, 65*(3), 153-157. doi: 10.1136/oem.2007.034983

Dobson, A. J. (2002). *An Introduction to Generalized Linear Models*. London: Chapman & Hall/CRC.

Falconer, D.S. (1965). Inheritance of liability to certain diseases estimated from incidence among relatives. *Annual of Human Genetics, 29*, 51-76.

Gjerde, L. C., Czajkowski, N., Roysamb, E., Orstavik, R. E., Knudsen, G. P., Ostby, K., Torgersen, S., Myers, J., Kendler, K. S., & Reichborn-Kjennerud, T. (2012). The heritability of avoidant and dependent personality disorder assessed by personal interview and questionnaire. *Acta Psychiatrica Scandinavica, 126*(6), 448-457.

Gjerde, L. C., Knudsen, G. P., Czajkowski, N., Gillespie, N., Aggen, S. H., Røysamb, E., Reichborn-Kjennerud, T., Tambs, K., Kendler, K. S., & Ørstavik, R. E. (2013). Genetic and environmental contributions to long-term sick leave and disability pension: a population-based study of young adult Norwegian twins. *Twin Research and Human Genetics, 16*(4), 759-766.

Gjesdal, S., & Bratberg, E. (2003). Diagnosis and duration of sickness absence as predictors for disability pension: Results from a three-year multi-register based and prospective study. *Scandinavian Journal of Public Health, 31*, 246-254.

Gjesdal, S., Haug, K., & Ringdal, P. R. (2005). The risk of disability pension among young persons on long-term sick leave. *Tidsskrift for Den Norske Lægeforeningen*(125), 1801-1805.

Grant, B. F., Chou, S. P., Goldstein, R. B., Huang, B., Stinson, F. S., Saha, T. D., Smith, S. M., Dawson, D. A., Pulay, A. J., Pickering, R. P., & Ruan, W. J. (2008). Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: Results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. [Review]. *Journal of Clinical Psychiatry, 69*(4), 533-545.

Henderson, M., Harvey, S. B., Overland, S., Mykletun, A., & Hotopf, M. (2011). Work and common psychiatric disorders. [Review]. *Journal of the Royal Society of Medicine, 104*(5), 198-207.

Hensing, G., Andersson, L., & Brage, S. (2006). Increase in sickness absence with psychiatric diagnosis in Norway: a general population-based epidemiologic study of age, gender and regional distribution. *Bmc Medicine, 4*. doi: 19

10.1186/1741-7015-4-19

Holm, A. L., & Severinsson, E. (2008). The emotional pain and distress of borderline personality disorder: A review of the literature. [Review]. *International Journal of Mental Health Nursing, 17*(1), 27-35.

Huang, Y. , Kotov, R. , de Girolamo, G. , Preti, A., Angermeyer, M., Benjet, C., Demyttenaere, K., de Graaf, R., Gureje, O., Nasser Karam, A., Lee, S., Le´ pine, J. P., Matschinger, H., Posada-Villa, J., Suliman, S., Vilagut, G., & Kessler, R. C. (2009). DSM–IV personality disorders in the WHO World Mental Health Surveys. *The British Journal of Psychiatry, 195*, 46-53.

Hultin, H., Lindholm, C., & Moller, J. (2012). Is There an Association between Long-Term Sick Leave and Disability Pension and Unemployment beyond the Effect of Health Status? - A Cohort Study. *Plos One, 7*(4). doi: e35614. 10.1371

Jinks, J. L., & Fulker, D. W. (1970). Comparison of biometrical genetical, MAVA, and classical approaches to analysis of human behavior. *Psychological Bulletin, 73*(5), 311-349.

Kendler, K. S., Aggen, S. H., Czajkowski, N., Roysamb, E., Tambs, K., Torgersen, S., Neale, M. C., & Reichborn-Kjennerud, T. (2008). The Structure of Genetic and Environmental Risk Factors for DSM-IV Personality Disorders A Multivariate Twin Study. *Archives of General Psychiatry, 65*(12), 1438-1446.

Kendler, K. S., Aggen, S. H., Knudsen, G. P., Roysamb, E., Neale, M. C., & Reichborn-Kjennerud, T. (2011). The Structure of Genetic and Environmental Risk Factors for

Syndromal and Subsyndromal Common DSM-IV Axis I and All Axis II Disorders. *American Journal of Psychiatry, 168*(1), 29-39.

Kendler, K. S., Neale, M. C., MacLean, C. J., Heath, A. C., Eaves, L. J., & Kessler, R. C. (1993). Smoking and major depression. A causal analysis. *Archives of General Psychiatry, 50*(1), 36-43.

Kendler, K.S., Czajkowski, Nikolai, Tambs, Kristian, Torgersen, Svenn, Aggen, Steven H., Neale, Michael C., & Reichborn-Kjennerud, Ted. (2006). Dimensional representations of DSM-IV Cluster A personality disorders in a population-based sample of Norwegian twins: A multivariate study. *Psychological Medicine, 36*(11), 1583-1591.

Kendler, K.S., Myers, J., Torgersen, S., Neale, M. C., & Reichborn-Kjennerud, T. (2007). The heritability of cluster A personality disorders assessed by both personal interview and questionnaire. *Psychological Medicine, 37*(5), 655-665.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication.[see comment][erratum appears in Arch Gen Psychiatry. 2005 Jul;62(7):768 Note: Merikangas, Kathleen R [added]]. *Archives of General Psychiatry, 62*(6), 593-602.

Knudsen, A. K., Harvey, S. B., Mykletun, A., & Overland, S. (2013). Common mental disorders and long-term sickness absence in a general working population. The Hordaland Health Study. *Acta Psychiatrica Scandinavica, 127*(4), 287-297.

Knudsen, A. K., Skogen, J. C., Harvey, S. B., Stewart, R., Hotopf, M., & Moran, P. (2012). Personality disorders, common mental disorders and receipt of disability benefits: evidence from the British National Survey of Psychiatric Morbidity. *Psychological Medicine, 42*(12), 2631-2640.

Lenzenweger, M. F., Lane, M. C., Loranger, A. W., & Kessler, R. C. (2007). DSM-IV personality disorders in the National Comorbidity Survey Replication. *Biological Psychiatry, 62*(6), 553-564.

Ligthart, L., & Boomsma, D. I. (2012). Causes of Comorbidity: Pleiotropy or Causality? Shared Genetic and Environmental Influences on Migraine and Neuroticism. *Twin Research and Human Genetics, 15*(2), 158-165.

Livesley, W. J., & Jang, K. L. (2000). Toward an empirically based classification of personality disorder. *Journal of Personality Disorders, 14*(2), 137-151.

Magnus, P., Berg, K., & Nance, W. E. (1983). Predicting zygosity in Norwegian twin pairs born 1915-1960. *Clinical Genetics, 24*, 103-112.

Marinangeli, M. G., Butti, G., Scinto, A., Di Cicco, L., Petruzzi, C., Daneluzzo, E., & Rossi, A. (2000). Patterns of comorbidity among DSM-III-R personality disorders. *Psychopathology, 33*(2), 69-74.

Martin, N. G., & Eaves, L. J. (1977). The genetical analysis of covariance structure. *Heredity, 38*(2), 79-95.

McCrae, R. R., Lockenhoff, C. E., & Costa, P. T. (2005). A step toward DSM-V: Cataloguing personality-related problems in living. *European Journal of Personality, 19*(4), 269-286.

McCrae, R.R, & Costa, Jr Paul T. . (1990). *Personality in Adulthood*. New York, NY: Guilford Press.

Michon, H. W. C., ten Have, M., Kroon, H., van Weeghel, J., de Graav, R., & Schene, A. H. (2008). Mental disorders and personality traits as determinants of impaired work functioning. *Psychological Medicine, 38*(11), 1627-1637.

Moncrieff, J., & Pomerleau, J. (2000). Trends in sickness benefits in Great Britain and the contribution of mental disorders. *Journal of Public Health Medicine, 22*(1), 59-67.

Nakao, K., Gunderson, J. G., Phillips, K. A., Tanaka, N., Yorifuji, K., Takaishi, J., & Nishimura, T. (1992). Functional impairment in personality disorders. *Journal of Personality Disorders, 6*(1), 24-33.

Neale, M. C. (2003). A finite mixture distribution model for data collected from twins. *Twin Research, 6*(3), 235-239.

Neale, M. C., & Kendler, K. S. (1995). Models of comorbidity for multifactorial disorders. *Am J Hum Genet, 57*(4), 935-953.

Neale, M. C., Roysamb, E., & Jacobson, K. (2006). Multivariate genetic analysis of sex limitation and G x E interaction. *Twin Research & Human Genetics: the Official Journal of the International Society for Twin Studies, 9*(4), 481-489.

Neale, M.C., & Cardon, L.R. (1992). *Methodology for genetic studies of twins and families*. Dordrecht, the Netherlands: Kluwer Academic Publishers.

Neale, M.C., & Maes, H.H. (2000). *Methodology for genetic studies of twins and families*. Dordrecht: Kluwer Akademic Publisher B.V.

Noren, K., Lindgren, A., Haellstom, T., Thormaehlen, B., Vinnars, B., Wennberg, P., Weinryb, R. M., & Barber, J. P. (2007). Psychological distress and functional impairment in patients with personality disorders. *Nordic Journal of Psychiatry, 61*(4), 260-270.

NOU. (Norwegian Official Reports 2000:27). Sykefravær og uførepensjonering - Et inkluderende arbeidsliv [Sickness absence and disability pensioning - a labour market for all]. Oslo: Norway.

OECD. (2010). Sickness, disability and work. Breaking the barriers. A synthesis of findings across OECD countries. Paris: OECD Publishing.

Pfohl, B. Blum, & Zimmerman, M. (1995). *Structured Interview for DSM-IV Personality (SIDP-IV)*. Iowa City: University of Iowa, Department of Psychiatry.

Reichborn-Kjennerud, T., Czajkowski, N., Neale, M. C., Orstavik, R. E., Torgersen, S., Tambs, K., Roysamb, E., Harris, J. R., & Kendler, K. S. (2007). Genetic and environmental influences on dimensional representations of DSM-IV cluster C personality disorders: a population-based multivariate twin study. *Psychological Medicine, 37*(5), 645-653.

Roysamb, E., Kendler, K. S., Tambs, K., Orstavik, R. E., Neale, M. C., Aggen, S. H., Torgersen, S., & Reichborn-Kjennerud, T. (2011). The Joint Structure of DSM-IV Axis I and Axis II Disorders. *Journal of Abnormal Psychology, 120*(1), 198-209.

Skodol, A. E., Johnson, J. G., Cohen, P., Sneed, J. R., & Crawford, T. N. (2007). Personality disorder and impaired functioning from adolescence to adulthood. *British Journal of Psychiatry, 190*, 415-420.

Soderberg, E., & Alexanderson, K. (2003). Sickness certification practices of physicians: A review of the litterature. *Scandinavian Journal of Public Health, 31*, 460-474.

SSB. (2013). Statistics Norway Statbank: Population´s level of education Retrieved November 26th, 2013, from http://ssb.no/en/utdanning/statistikker/utniv

Stormer, S., & Fahr, R. (2013). Individual determinants of work attendance: evidence on the role of personality. *Applied Economics, 45*(19), 2863-2875.

Suvisaari, J., Aalto-Setala, T., Tuulio-Henriksson, A., Harkanen, T., Saarni, S. I., Perala, J., Schreck, M., Castaneda, A., Hintikka, J., Kestila, L., Lahteenmaki, S., Latvala, A., Koskinen, S., Marttunen, M., Aro, H., & Lonnqvist, J. (2009). Mental disorders in young adulthood. *Psychological Medicine, 39*(2), 287-299.

Svedberg, P., Ropponen, A., Alexanderson, K., Lichtenstein, P., & Narusyte, J. (2012). Genetic susceptibility to sickness absence is similar among women and men: Findings from a Swedish twin cohort. *Twin Research and Human Genetics, 15*(5), 642-648.

Tambs, K., Ronning, T., Prescott, C. A., Kendler, K. S., Reichborn-Kjennerud, T., Torgersen, S., & Harris, J. R. (2009). The Norwegian Institute of Public Health twin study of mental health: examining recruitment and attrition bias. *Twin Research and Human Genetics, 12*(2), 158-168.

Torgersen, S., Czajkowski, N., Jacobson, K., Reichborn-Kjennerud, T., Roysamb, E., Neale, M. C., & Kendler, K. S. (2008). Dimensional representations of DSM-IV cluster B personality disorders in a population-based sample of Norwegian twins: a multivariate study. *Psychological Medicine, 38*(11), 1617-1625.

Torgersen, S., Myers, J., Reichborn-Kjennerud, T., Røysamb, E., Kubarych, T., & Kendler, K.S. (2012). The heritability of Cluster B personality disorders assessed both by personal interview and questionnaire. *Journal of Personality Disorders, 26*(6), 848-866.

Trull, Timothy J., & Durrett, Christine A. (2005). Categorical and dimensional models of personality disorder. *Annual Review of Clinical Psychology, 1*(1), 355-380.

Vaez, M., Rylander, G., Nygren, A., Asberg, M., & Alexanderson, K. (2007). Sickness absence and disability pension in a cohort of employees initially on long-term sick leave due to psychiatric disorders in Sweden. *Social Psychiatry and Psychiatric Epidemiology, 42*(5), 381-388.

Vlasveld, M.C., van der Feltz-Cornelis, C.M., Anema, J.R., van Mechelen, W., Beekman, A.T., van Marwijk, H.W., & Penninx, B.W. (2012). The Associations Between Personality Characteristics and Absenteeism: A Cross-Sectional Study in Workers With and Without Depressive and Anxiety Disorders. *Journal of Occupational Rehabilitation, 23*, 309-317.

Widiger, T. A., & Mullins-Sweatt, S. N. (2009). Five-factor model of personality disorder: a proposal for DSM-V. *Annu Rev Clin Psychol, 5*, 197-220.

Widiger, T. A., & Trull, T. J. (2007). Plate tectonics in the classification of personality disorder - Shifting to a dimensional model. [Review]. *American Psychologist, 62*(2), 71-83.

Østby, K. A., Czajkowski, N., Knudsen, G.P., Gjerde, L. C., Kendler, K.S., Ørstavik, R.E., & Reichborn-Kjennerud, T. (submitted). Personality disorders are an important risk factor for disability pensioning *Social Psychiatry & Psychiatric Epidemiology*

Table 1.

Results from ordinal logistic regression analyses: Odds ratios for LTSL (sick leave >16 days) by dimensionally measured PD traits[a]

	Model 1 Adjusted for sex	**Model 2** Adjusted for sex and all significant PDs
Variables	**OR (95% CI)**	**OR (95% CI)**
Paranoid PD	1.21 (1.12-1.30)***	1.11 (1.01-1.21)*
Schizoid PD	1.04 (0.92-1.16)	
Schizotypal PD	1.36 (1.22-1.52)***	1.19 (1.05-1.36)**
Antisocial PD	1.10 (0.98-1.23)	
Borderline PD	1.23 (1.13-1.34)***	1.13 (1.03-1.25)*
Histrionic PD	1.07 (1.00-1.14)*	0.96 (0.89-1.03)
Narcissistic PD	1.03 (0.96-1.10)	
Avoidant PD	1.12 (1.05-1.19)**	1.01 (0.94-1.09)
Dependent PD	1.17 (1.09-1.25)***	1.07 (0.99-1.17)
Obsessive-compulsive PD	1.07 (1.01-1.12)*	1.00 (0.95-1.06)

***=significant at p<0.001, **=significant at p<0.01, *=significant at p<0.05
[a]PDs traits are summed and truncated into 3-5 categories

Table 2.

Tetravariate model fitting results for STPD, PPD, BPD and LTSL

Model	-2LL	df	p	AIC
1. ACE CSL	33,914.94	15,786	-	2,342.94
2. AE CSL	33,940.53	15,800	0.03	2,340.53
3. CE CSL	33,983.47	15,800	<0.00	2,383.47
4. E CSL	36,068.84	15,814	<0.00	4,440.84
5. ACE NSL	33,944.60	15,800	0.01	2,344.60
6. AE NSL	**33,953.72**	**15,810**	**0.03**	**2,333.72**
7. CE NSL	34,045.77	15,810	<0.00	2,425.77
8. E NSL	36,336.90	15,820	<0.00	4,696.90

Best fitting model in bold type, STPD=schizotypal personality disorder, PPD=paranoid personality disorder, BPD=borderline personality disorder, LTSL=long-term sick leave, CSL=common sex limitation model, NSL=no sex limitation model

Table 3.

Genetic and environmental correlations

	STPD	**PPD**	**BPD**	**LTSL**
STPD		+0.56 (0.48-0.62)	+0.43 (0.34-0.51)	**+0.07** (0.00-0.17)
PPD	+0.62 (0.39-0.87)		+0.41 (0.32-0.49)	**+0.05** (0.00-0.14)
BPD	+0.39 (0.16-0.61)	+0.61 (0.39-0.82)		**+0.08** (0.01-0.16)
LTSL	**+0.40** (0.21-0.63)	**+0.39** (0.23-0.56)	**+0.24** (0.12-0.36)	

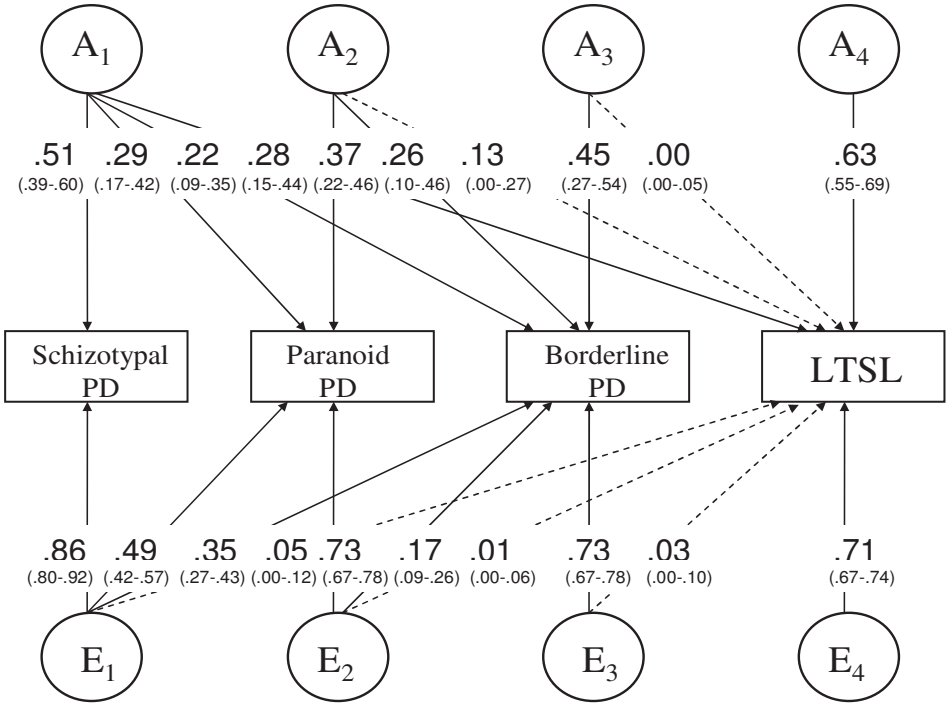
The genetic correlations between the PDs and LTSL are shown in the lower triangle, and the environmental correlations are shown in the upper triangle. LTSL = long-term sick leave, STPD = schizotypal personality disorder, PPD = paranoid personality disorder, BPD = borderline personality disorder.

FIGURE LEGENDS

Figure 1.

Best fitting tetravariate Cholesky model for schizotypal personality disorder, paranoid personality disorder, borderline personality disorder and long-term sick leave (LTSL) with parameter estimates and confidence intervals. Dotted lines indicate non-significant effects.

Figure 1.


A1
A2
A3
A4
.51 (.39-.60)
.29 (.17-.42)
.22 (.09-.35)
.28 (.15-.44)
.37 (.22-.46)
.26 (.10-.46)
.13 (.00-.27)
.45 (.27-.54)
.00 (.00-.05)
.63 (.55-.69)
Schizotypal PD
Paranoid PD
Borderline PD
LTSL
.86 (.80-.92)
.49 (.42-.57)
.35 (.27-.43)
.05 (.00-.12)
.73 (.67-.78)
.17 (.09-.26)
.01 (.00-.06)
.73 (.67-.78)
.03 (.00-.10)
.71 (.67-.74)
E1
E2
E3
E4

APPENDICES

APPENDIX 1

The Q2 questionnaire (items 88 to 178 comprises the Dysfunctional Personality Questionnaire)

Spørreskjema for tvillinger

33251

1 Hvem ble født først?

☐ Du ☐ Din tvilling

Spørsmål 2 - 5 *fylles bare ut av tvillinger med samme kjønn*

2 Var du og din tvillingsøster/-bror like som to dråper vann i barndommen eller var dere bare så like som søsken flest?

☐ Som to dråper vann ☐ Som søsken flest ☐ Vet ikke

3 Hadde noen av følgende personer problemer med å se forskjell mellom deg og din tvilling da dere var barn?

	Ofte	Av og til	Aldri	Vet ikke
Nærmeste familie:	☐	☐	☐	☐
Fremmede:	☐	☐	☐	☐

4 Kryss av hvor like du og din tvilling var når det gjelder:

	Helt like	Nesten like	Forskjellige	Vet ikke
Hårfarge:	☐	☐	☐	☐
Hårtype:	☐	☐	☐	☐
Farge på øynene:	☐	☐	☐	☐
Stemme:	☐	☐	☐	☐
Fingerferdighet:	☐	☐	☐	☐

5 Tror du selv at du og din tvilling er:

☐ Eneggede ☐ Toeggede ☐ Vet ikke

6 Hvor høy er du?

m cm

7 Hvor mye veier du?

kg (Hvis du er gravid, oppgi din vekt da du ble gravid)

8 Når ble du født?

Dag Måned År

OM DIN HELSE

9 Hvordan er din helse for tiden?

☐ Dårlig ☐ Ikke helt god ☐ God ☐ Svært god

10 Sammenlignet med din tvilling, hvordan er helsen din for tiden?

☐ Mye verre ☐ Litt bedre
☐ Litt verre ☐ Mye bedre
☐ Like god

11 Hvordan vil du beskrive din helse nå, hvis du sammenligner den med hvordan den var for tre år siden?

☐ Mye bedre nå enn for tre år siden
☐ Noe bedre nå enn for tre år siden
☐ Omtrent det samme som for tre år siden
☐ Noe verre enn for tre år siden
☐ Mye verre enn for tre år siden

12 Hvor mye har problemer med din fysiske- eller psykiske helse hindret deg i arbeidet eller i dine daglige sosiale aktiviteter med familie eller venner de siste 4 ukene?

	Fysisk	Psykisk
Ikke i det hele tatt	☐	☐
Litt	☐	☐
Noe	☐	☐
En god del	☐	☐
Svært mye	☐	☐

13 Har du, eller har du hatt noen av følgende sykdommer eller helseproblemer?

	Hvis ja, kryss av	Hvis ja, husker du hvor gammel du var ved første tegn på sykdom eller plager?	Hvis du ble frisk eller kvitt plagene, ved hvilken alder skjedde det?
Høysnue	☐	år	år
Elveblest	☐	år	år
Astma	☐	år	år
Nikkelallergi	☐	år	år
Barne/atopisk eksem	☐	år	år
Psoriasis	☐	år	år
Annen eksem/hudlidelse	☐	år	år
Migrene	☐	år	år
Annen hyppig hodepine	☐	år	år
Stadig verking eller svie øverst i magen	☐	år	år
Tykktarmskatarr (diare, treg mage, takvise smerter)	☐	år	år
Påvist kronisk tarmsykdom (Crohns eller ulcerøs kolitt)	☐	år	år
Søvnproblemer	☐	år	år
Sukkersyke (diabetes)	☐	år	år
Epilepsi	☐	år	år
Nærsynthet	☐	år	år
Langsynthet	☐	år	år
Skjeve hornhinner	☐	år	år
Gjentatte infeksjoner i øret	☐	år	år
Gjentatte infeksjoner i mandler	☐	år	år
Gjentatte infeksjoner i bihule	☐	år	år
Blærekatarr	☐	år	år
Gjentatte nakke- og skuldersmerter	☐	år	år
Smerter i korsryggen	☐	år	år
Langvarige muskelsmerter	☐	år	år
Fibromyalgi	☐	år	år
Bechterews sykdom	☐	år	år
Leddgikt	☐	år	år
Ofte svimmel	☐	år	år
Hyperaktivitet	☐	år	år
MBD	☐	år	år
Andre langvarige sykdommer eller helseproblemer	☐	år	år

Hvis ja, beskriv:

14 **Har du eller en i nærmeste familie hatt denne tilstanden eller sykdommen?**

	Nei	Vet ikke	Ja	Hvis ja, hvilke familiemedlemmer har hatt tilstanden eller sykdommen? Jeg selv	Mor	Far	Tvilling	Bror	Søster	Sønn	Datter
Feberkramper	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Andre former for kramper eller rykninger	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Epilepsi (fallesyke)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Bevissthetstap uten rykninger eller kramper	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Om luftveisplager

15 **Har du noen gang hatt tung pust eller piping/surkling/ tetthet i brystet?**
☐ Ja ☐ Nei, gå til spørsmål 20

16 **Har du noen gang hatt tung pust eller piping/surkling/ tetthet i brystet i løpet av *de siste 12 månedene?***
☐ Ja ☐ Nei, gå til spørsmål 20

17 **Hvor mange anfall med tung pust eller piping/surkling/ tetthet i brystet har du hatt i løpet av *de siste 12 månedene?***
☐ Ingen ☐ 1 til 3 ☐ 4 til 12 ☐ Mer enn 12

18 **Hvor ofte i gjennomsnitt har søvnen blitt forstyrret på grunn av tung pust eller piping/surkling/tetthet i brystet de siste 12 månedene?**
☐ Aldri våknet
☐ Mindre enn en natt pr. uke
☐ En eller flere netter pr. uke

19 **Har piping/surkling/tetthet i brystet eller tung pust vært så alvorlig *de siste 12 månedene* at du har hatt problemer med å snakke, slik at du bare har kunnet si ett eller to ord mellom hver pust?**
☐ Ja ☐ Nei

20 **Har du i løpet av *de siste 12 månedene* hatt tung pust eller piping/surkling/tetthet i brystet under eller etter fysisk trening eller mosjonering?**
☐ Ja ☐ Nei

21 **Har du i løpet av *de siste 12 måndene* hatt tørr hoste om natten uten å være forkjølet eller ha annen luftveisinfeksjon?**
☐ Ja ☐ Nei

22 **Bruker du faste medisiner mot astma?**
☐ Ja ☐ Nei

23 **Hvis ja, bruker du inhalasjonssteroider som Becotide, Pulmicort, Viarox, Flutide, Flunitec eller lignende?**
☐ Ja ☐ Nei

Om utslett

24 **Har du noen gang hatt kløende utslett som har kommet og gått i minst 6 måneder?**
☐ Ja ☐ Nei, gå til spørsmål 29 «Om neseplager»

25 **Har du noen gang hatt dette kløende utslettet i løpet av de siste 12 månedene?**
☐ Ja ☐ Nei, gå til spørsmål 29, «Om neseplager»

26 **Har dette kløende utslettet noen gang sittet på noen av de følgende stedene: albuebøyene (på innsiden), bak knærne, foran på anklene, under baken eller rundt hals, ører eller øyne?**
☐ Ja ☐ Nei

27 **Har dette utslettet vært helt borte noen gang i løpet av de siste 12 månedene?**
☐ Ja ☐ Nei

28 **I løpet av de siste 12 månedene, hvor ofte i gjennomsnitt har du blitt holdt våken om natten på grunn av dette kløende utslettet?**
☐ Ingen ganger de siste 12 månedene
☐ Mindre enn en natt pr. uke
☐ En eller flere netter pr. uke

Om neseplager

Alle spørsmål er om problemer som oppstår når du **IKKE** er forkjølet.

29 **Har du noen gang hatt problemer med nysing, eller rennende eller tett nese når du IKKE har vært forkjølet eller har hatt influensa?**
☐ Ja ☐ Nei, gå til spørsmål 34, «Om ørebetennelser»

30 **I løpet av de siste 12 månedene, har du da hatt problemer med nysing eller rennende eller tett nese UTEN å ha vært forkjølet eller å ha hatt influensa?**
☐ Ja ☐ Nei, gå til spørsmål 34, «Om ørebetennelser»

31 **I løpet av de siste 12 månedene, har disse nese-problemene vært ledsaget av kløende, rennende øyne?**
☐ Ja ☐ Nei

32 **I hvilke av de siste 12 månedene har du hatt neseproblemer?** (Sett kryss for hver måned som passer)

☐ Januar	☐ April	☐ Juli	☐ Oktober
☐ Februar	☐ Mai	☐ August	☐ November
☐ Mars	☐ Juni	☐ September	☐ Desember

33 **I løpet av de siste 12 månedene, hvor mye har disse neseproblemene virket inn på din daglige aktivitet?**
☐ Ikke i det hele tatt ☐ Litt ☐ Mye ☐ Veldig mye

Om ørebetennelser

Hvis du ***ikke*** har hatt ørebetennelse ***før du begynte på skolen,*** gå til spørsmål 37 «Om psoriasis».

34 **Hvis du hadde ørebetennelser, omtrent hvor ofte tror du at du hadde det?**
☐ 2 - 4 episoder i løpet av året
☐ En episode i året
☐ Mindre enn en episode i året
☐ Vet ikke

33251

35 **Ble du tatt med til lege for problemer med ørene eller hørselen?** Kryss av for både «vanlig» lege og øre-nese-hals spesialist (i og utenfor sykehus)

	Lege	Spesialist
Nei, aldri	☐	☐
1 gang	☐	☐
2 - 4 ganger	☐	☐
5 eller flere ganger	☐	☐
Vet ikke	☐	☐

36 **Vet du om følgende undersøkelser/behandlinger ble gjort?** (Hvis du ikke vet nøyaktig, oppgi det du tror) (Sett ett eller flere kryss)

- ☐ Ingen behandling
- ☐ Stukket hull i trommehinnen
- ☐ Fjernet falsk mandel/polypp
- ☐ Annet
- ☐ Antibiotika
- ☐ Innlagt dren (ventilasj.rør)
- ☐ Fjernet benvev bak øret
- ☐ Vet ikke

Om psoriasis

Hvis du ***ikke*** har hatt psoriasis, gå til spørsmål 41 «Om annet»

37 **Om du har eller har hatt psoriasis, er diagnosen bekreftet av hudspesialist?**

☐ Ja ☐ Nei

Hvilken beskrivelse passer best til din psoriasis før og nå? (Kun ett kryss i hver kolonne)

	Første utbrudd	Siste 12 mndr.	Siste 14 dager
A. Akutt (plutselig) utbrudd av bitte-små flekker over hele kroppen	☐	☐	☐
B. Flekker på albuer/knær/hodebunn som kommer av og til	☐	☐	☐
C. Flekker på albuer/knær/hodebunn som er nærmest konstant tilstede	☐	☐	☐
D. Som C, men også enkelte flekker på overkroppen	☐	☐	☐
E. Utslett på større områder på kropp/armer/ben/ansikt som kommer av og til	☐	☐	☐
F. Utslett på større områder på kropp /armer/ben/ansikt som er konstant tilstede	☐	☐	☐
G. Har ikke hatt tegn til psoriasis		☐	☐

38 **Har du negleforandringer?**

- ☐ Ja, kun som små punkter i neglene
- ☐ Ja, med fortykkelse eller løsning av neglene
- ☐ Nei

39 **Her er listet opp noen faktorer som kan tenkes å utløse eller forverre psoriasis. Kryss av for hva som passer for ditt første utbrudd, ditt siste utbrudd (oppbluss) og hva som forverrer din psoriasis generelt.** (Sett ett eller flere kryss)

	Første utbrudd	Siste utbrudd	Generell forverring
Halsinfeksjon	☐	☐	☐
Annen infeksjon	☐	☐	☐
Stress/psykisk påkjenning	☐	☐	☐
Solforbrenning	☐	☐	☐
Alkohol	☐	☐	☐
Tobakk	☐	☐	☐
Svangerskap	☐	☐	☐
Medisin:	☐	☐	☐
Annet:	☐	☐	☐
Ikke noe spesielt	☐	☐	☐
Husker ikke	☐	☐	☐

40 **Angi hvor ofte du har benyttet følgende behandlinger de siste 12 månedene?**

	Antall avgrensede perioder				
	Ingen	1	2 - 3	4 eller flere	Alltid/ nesten alltid
Fuktighetskrem	☐	☐	☐	☐	☐
Kortisonkrem/salve	☐	☐	☐	☐	☐
Andre kremer/salver	☐	☐	☐	☐	☐
Lysbehandling	☐	☐	☐	☐	☐
Sydenreiser	☐	☐	☐	☐	☐
Tabletter	☐	☐	☐	☐	☐
Annet	☐	☐	☐	☐	☐

Annet

41 **Har du noen gang vært plaget av stamming?**

☐ Ja ☐ Nei ☐ Vet ikke

42 **Har du, eller har du hatt spesielle lese- eller skriveproblemer?**

Lesing: ☐ Store problemer ☐ Noen problemer ☐ Ingen
Skriving: ☐ Store problemer ☐ Noen problemer ☐ Ingen

43 **Hvis du bruker briller eller kontaktlinser, hvilken styrke bruker du?** (Hvis forskjell på øynene, oppgi sterkeste)

Langsynt: + , ☐ Vet ikke
Nærsynt: - , ☐ Vet ikke

44 **Hvilken hånd bruker du til å:**

	Høyre	Venstre	Begge
skrive med	☐	☐	☐
skjære brød med	☐	☐	☐

45 **Hvor ofte har du brukt noen av disse medisinene den siste måneden?**

	Daglig	Hver uke	Sjelden	Aldri
Avslappende/beroligende	☐	☐	☐	☐
Sovemedisin	☐	☐	☐	☐
Smertestillende	☐	☐	☐	☐

Spørsmål 46 - 49 skal kun besvares av kvinner

46 **Er du gravid nå?**

☐ Ja ☐ Nei ☐ Vet ikke

47 **Hvor gammel var du da du fikk din første menstruasjon?**

år

48 **Er menstruasjonen til vanlig regelmessig (samme antall dager fra mens til mens?**

- ☐ Ja, ca dager fra første dag i en til første dag i neste
- ☐ Nei
- ☐ Har ikke mens

49 **Har det noen gang gått minst 3 måneder uten menstruasjon uten at du har vært gravid eller har brukt prevensjon (p-sprøyte, p-piller, hormonspiral)?**

☐ Ja ☐ Nei

50 **Får du kløende utslett av ørepynt/smykker, klokke eller annet metall som kommer i kontakt med huden?**

☐ Ja ☐ Nei ☐ Vet ikke

51 **Har du plager eller reagerer du på noe av det som er nevnt under?** Kryss av for hva slags plager du har for hver ting. (Sett ett eller flere kryss for hver linje)

	Nese-plager	Øye plager	Eksem plager	Mage plager	Astma/ pusteplager
Hund	☐	☐	☐	☐	☐
Katt	☐	☐	☐	☐	☐
Andre dyr	☐	☐	☐	☐	☐
Gress/Trær	☐	☐	☐	☐	☐
Burot	☐	☐	☐	☐	☐
Husstøv	☐	☐	☐	☐	☐
Muggsopp	☐	☐	☐	☐	☐
Infeksjoner	☐	☐	☐	☐	☐
Melkeprodukter	☐	☐	☐	☐	☐
Sjokolade	☐	☐	☐	☐	☐
Nøtter	☐	☐	☐	☐	☐
Skalldyr	☐	☐	☐	☐	☐
Røyk	☐	☐	☐	☐	☐
Parfyme/maling etc.	☐	☐	☐	☐	☐
Kulde	☐	☐	☐	☐	☐
Fysisk aktivitet	☐	☐	☐	☐	☐

Annet , beskriv:

LIVSSTIL

52 **Røyker du for tiden?**

☐ Nei Totalt

☐ Ja, daglig (oppgi gj.snitt. ant. sigaretter pr. dag)

☐ Ja, av og til (oppgi gj.snitt. ant. sigaretter pr. uke)

53 **Hvis du noen gang har røykt, hvor gammel var du da du begynte å røyke daglig?**

år

54 **Hvis du har sluttet å røyke, hvor gammel var du da?**

år

55 **Hvor ofte har du drukket alkohol (øl, vin eller brennevin) *de siste 14 dagene?***

☐ Jeg har ikke drukket alkohol, men er ikke totalavholdende
☐ Jeg har drukket 1 - 4 ganger
☐ Jeg har drukket 5 - 10 ganger
☐ Jeg har drukket mer enn 10 ganger
☐ Jeg er totalavholdende, drikker aldri alkohol

56 **Dersom du har drukket alkohol de siste 14 dagene, har det ført til at du noen gang har følt deg beruset?**

☐ Ja ☐ Nei

57 **Hvor ofte hender det at du drikker så mye alkohol at det tilsvarer 5 halvflasker øl eller 1 helflaske rød-/hvitvin eller 1/2 flaske hetvin eller en 1/4 flaske brennevin?**

☐ 0 - 4 ganger i året ☐ 1 - 2 ganger i uka
☐ 5 - 10 ganger i året ☐ 3 - 5 ganger i uka
☐ 1 - 3 ganger i måneden ☐ 6 ganger eller mer i uka

58 **Har det vært perioder i livet da du har drukket for mye, eller i hvert fall i meste laget?**

☐ Ja ☐ I tvil, kanskje ☐ Nei

59 **Hvor gammel var du da du første gang følte deg påvirket av alkohol i selskap eller blant venner?**

år ☐ Har aldri vært påvirket

60 **Hvor ofte driver du mosjon (f.eks. går tur, går på ski eller driver trening/idrett)?**

☐ Aldri ☐ 1 - 2 ganger i uka
☐ Sjeldnere enn en gang i uka ☐ 3 ganger i uka eller mer

61 **Hvis du driver mosjon, hvor hardt mosjonerer du?**

☐ Blir ikke andpusten og svett
☐ Blir andpusten og svett
☐ Tar meg nesten helt ut

62 **I tilfelle, hvor lenge holder du på hver gang?**

☐ Mindre enn 15 minutter ☐ 30 minutter - 1 time
☐ 16 - 29 minutter ☐ Mer enn 1 time

63 **Hvis du driver eller har drevet idrett, kryss av for type idrettsaktivitet**

☐ Utholdenhetsidrett (løp, langrenn etc.)
☐ Lagidrett (fotball, håndball etc.)
☐ Estetisk idrett (dans, turn etc.)
☐ Styrkeidrett (styrkeløft, bryting, etc.)
☐ Kampidrett (judo, karate etc.)
☐ Annet

64 **Hvis du har drevet aktiv idrett, omtrent hvor mange timer trener/trente du pr. uke i snitt i din mest aktive periode og hvor lenge holdt du på?**

☐ Under 5 timer
☐ 5 - 10 timer
☐ 11 - 20 timer
☐ Over 20 timer

Hvor gammel var du da du startet? år

Hvor gammel var du da du sluttet? år

Er fremdeles aktiv ☐

65 **Er det viktig for hva slags syn du har på deg selv at du holder en bestemt vekt?**

☐ Ja, svært viktig
☐ Ja, nokså viktig
☐ Nei, ikke særlig viktig

66 **Har det i løpet av de siste 6 månedene hendt at:**

du selv syntes at du var for tykk?

☐ Ja, en god del ☐ Ja, litt ☐ Nei

du var redd for å legge på deg eller bli for tykk?

☐ Ja, veldig ☐ Nokså ☐ Ikke særlig

andre sa du var for tynn, mens du selv synes du var for tykk?

☐ Ja, ofte ☐ Noen få ganger ☐ Nei

du følte at du mistet kontrollen mens du spiste og klarte ikke å stoppe før du hadde spist for mye?

☐ Ja, minst to ganger i uka ☐ 1 - 4 ganger i måneden ☐ Sjelden eller aldri

67 **Har du brukt oppkast, avføringsmidler, fastekurer eller hard fysisk trening for å kontrollere vekten?** (Sett kryss for hver ting du har brukt, og kryss av nedenfor hvor ofte det har skjedd).

	Minst to ganger i uka	1 - 4 ganger i måneden	Sjelden	Aldri
Oppkast	☐	☐	☐	☐
Avføringsmidler	☐	☐	☐	☐
Fastekurer	☐	☐	☐	☐
Hard fysisk trening	☐	☐	☐	☐

BAKGRUNN

68 Er du

☐ Ugift/ikke samboende ☐ Enke/enkemann
☐ Gift/samboende ☐ Separert/skilt

69 Hvor mange barn har du?

____ Barn ☐ Ingen barn

70 Hvilken utdanning har du utført, og hvilke utdannings-planer har du?
Oppgi bare høyeste utførte og planlagte utdannelse.

	Gjennomført	Planlagt
9-åring grunnskole	☐	☐
Grunnskolen 10. år	☐	☐
Videreg. skole, 1- 2 år	☐	☐
Videreg. skole, 3 år yrkesfaglig studieret.	☐	☐
Allmennfaglig eller økonomisk studieret., 3 år	☐	☐
Høyskole eller universitetet, mindre enn 4 år	☐	☐
Høyskole eller universitetet, 4 år eller mer	☐	☐

71 Hvor mange års utdannelse har du totalt? (Ved deltidsutdannelse, regn om til antall år tilsvarende det utdannelsen ville tatt på heltid)

____ år

72 Hvilket yrke har du? *(Bruk blokkbokstaver)*

73 Hvis du er under utdanning, hvilket yrke utdanner du deg til?

74 Hvor ofte har du hatt kontakt med din tvilling det siste året?

	Telefon	Personlig
Hver dag	☐	☐
1 - 3 ganger i uka	☐	☐
1 - 3 ganger i måneden	☐	☐
7 - 12 ganger i året	☐	☐
1 - 6 ganger i året	☐	☐
Sjeldnere enn 1 gang i året	☐	☐

75 Hvor god kontakt synes du at du har hatt med din tvilling, sett over hele livet? Sammenlign med hva du tror er vanlig for vanlige søsken.

☐ Dårligere ☐ Like god ☐ Litt bedre ☐ Mye bedre

76 Gikk du og din tvilling i samme klasse på skolen, og i så fall hvor lenge?

☐ Nei ☐ Ja ____ år

77 Hvis du har flyttet fra barndomshjemmet, hvor gammel var du da du flyttet?

____ år ☐ Ikke flyttet

78 Hvor mange år i alt har du og din tvilling bodd sammen?

____ år

79 Hvor langt er det mellom din egen og din tvillings bostedsadresse?

☐ Bor sammen ☐ 100 m - 1 km ☐ 1 mil - 10 mil
☐ 0 - 100 m ☐ 1 km - 1 mil ☐ Mer enn 10 mil

33251

PERSONLIGHET, TRIVSEL OG PSYKISKE PROBLEMER

80 Nedenfor er en liste over noen problemer eller plager. Kan du for hver av dem si om du de siste 14 dagene ikke var plaget, om du var litt, ganske mye eller veldig plaget.
(Husk å sette kryss for hver plage).

	Ikke plaget	Litt plaget	Ganske plaget	Veldig plaget
Stadig redd eller engstelig	☐	☐	☐	☐
Føler du deg anspent eller oppjaget	☐	☐	☐	☐
Følelse av håpløshet mht fremtiden	☐	☐	☐	☐
Nedtrykt, tungsindig	☐	☐	☐	☐
Mye bekymret eller urolig	☐	☐	☐	☐

81 Når du tenker på hvordan du har det for tiden, er du stort sett fornøyd med tilværelsen, eller er du stort sett misfornøyd?

☐ Særdeles fornøyd ☐ Både- og
☐ Meget fornøyd ☐ Nokså misfornøyd
☐ Nokså fornøyd ☐ Svært misfornøyd

82 Har du i løpet av siste måned vært plaget av nervøsitet (irritabel, urolig, anspent eller rastløs)?

☐ Nesten hele tiden ☐ Av og til
☐ Ofte ☐ Aldri

83 Føler du deg stort sett sterk og opplagt, eller trøtt og sliten?

☐ Meget sterk og opplagt ☐ Både- og
☐ Ganske sterk og opplagt ☐ Trøtt og sliten

84 Hender det ofte at du føler deg ensom?

☐ Meget ofte ☐ Av og til
☐ Ofte ☐ Sjelden eller aldri

85 Har du i løpet av siste måned hatt innsovnings- eller søvnproblemer?

☐ Nesten hver natt ☐ Av og til
☐ Ofte ☐ Aldri

86 Er du vanligvis glad eller nedstemt?

☐ Nedstemt
☐ Nokså nedstemt
☐ Både- og
☐ Nokså glad
☐ Glad

87 Har du noen gang søkt hjelp i helsevesenet for psykiske problemer?

☐ Ja ☐ Nei

Nedenfor er en del beskrivelser som passer mer eller mindre godt for forskjellige personer. Du synes kanskje det kan være litt vanskelig å besvare noen av spørsmålene, men gjør så godt du kan. Hvis det stort sett ikke stemmer, skal du sette kryss i boksen under «galt». Hvis du er enig i utsagnet, eller hvis det stort sett passer for deg skal du krysse av i boksen under «riktig».

		Galt	Riktig
88	Mine reaksjoner er mer bestemt av følelsene enn av fornuften	☐	☐
89	Jeg mister lett motet når tingene går galt	☐	☐
90	For meg er det viktigere enn noe annet at folk forstår meg og viser sympati og medfølelse	☐	☐
91	Jeg er temmelig jevn og stabil i mitt følelsesliv	☐	☐
92	Når jeg er sammen med andre mennesker, holder jeg meg gjerne i bakgrunnen	☐	☐
93	Jeg lar mine følelser få fritt utløp når jeg er sint	☐	☐
94	Jeg har det ikke med å gruble over hva folk har ment med den og den uttalelsen	☐	☐
95	Jeg handler som jeg føler	☐	☐
96	Vanligvis pleier jeg føle meg like sikker og trygg selv i helt nye og ukjente situasjoner	☐	☐
97	Jeg liker ikke å sløse med penger	☐	☐
98	Jeg har av og til en intens, ubehagelig følelse av at jeg er annerledes enn alle andre	☐	☐
99	Stort sett er jeg rolig og likevektig	☐	☐
100	Når jeg er sammen med flere mennesker, holder jeg meg ganske stille og taus	☐	☐
101	Det er sjelden jeg blir særlig opphisset	☐	☐
102	Jeg har alltid forsøkt å unngå sosialt samvær med andre mennesker	☐	☐
103	Jeg er litt av en rotekopp	☐	☐
104	I perioder har jeg tenkt at det er ingen mennesker som egentlig er glad i meg	☐	☐
105	Jeg har aldri hatt sans for å spare penger	☐	☐
106	Av og til synes jeg at jeg ikke er noe tess i det hele tatt	☐	☐
107	For lenge siden bestemte jeg meg for at det var best å ha lite med andre å gjøre	☐	☐
108	Når ting blir kjedelige, liker jeg å skape litt spenning	☐	☐
109	Jeg farer opp når situasjonen berettiger det	☐	☐
110	Jeg må sies å stå med begge bena på jorda. Jeg holder meg til det konkrete, isteden for å fortape meg i alle slags luftige fantasier	☐	☐
111	I konfliktsituasjoner hender det ofte at jeg er den som gir meg, enda jeg egentlig vet at det er jeg som har rett	☐	☐
112	Enkelte vil kunne betrakte meg som noe uvøren, jeg liker å ta sjanser, kaste meg ut i det, så får det heller gå som det går	☐	☐
113	Mange mennesker har spionert på mitt privatliv i flere år	☐	☐
114	Jeg har alltid gått i lange perioder omtrent uten å snakke med noen	☐	☐
115	Skjer det brått og uventede ting, kan jeg bli fullstendig forvirret	☐	☐
116	Min sinnsstemning forandrer seg lett alt etter hva som skjer rundt meg	☐	☐
117	I sosiale samvær er jeg nesten alltid anspent og ufri	☐	☐
118	Jeg kommer ofte med en uttalelse, for så å ønske at jeg kunne ta den tilbake igjen, fordi det jeg sa ikke var akkurat det jeg hadde ment	☐	☐
119	Jeg har lett for å kave meg alt for mye opp, selv for bagateller	☐	☐
120	Jeg ville virkelig like å være i showbusiness	☐	☐
121	Jeg er nok temmelig slurvete av meg	☐	☐
122	Min mangel på selvtillit kan av og til være en plage for meg	☐	☐
123	Fordi mine følelser skifter så hurtig, kan det ofte være svært vanskelig for meg å holde en fast linje i min tilværelse	☐	☐
124	Jeg har vanskelig for å slippe meg løs, selv i svært livlige selskaper	☐	☐
125	Det skal nokså mye til for å få meg sint	☐	☐
126	Jeg blir lett såret hvis jeg utsettes for spott eller nedsettende bemerkninger	☐	☐

33251

		Galt	Riktig
127	Det er vanskelig for meg å stole på folk etter som de så ofte vender seg mot meg eller lar meg i stikken	☐	☐
128	På en eller annen måte føler jeg at jeg ikke vet hvordan jeg skal oppføre meg sammen med andre mennesker	☐	☐
129	Jeg føler ofte at jeg forstiller meg, slik at folk ser meg som en helt forskjellig person til forskjellige tider.	☐	☐
130	Enkelte har hevdet, og muligens med rette, at jeg ikke er i stand til å styre penger	☐	☐
131	Jeg føler meg gjerne avslappet og rolig, selv når jeg er sammen med mennesker som har en betydelig høyere posisjon i samfunnet enn jeg selv	☐	☐
132	Folk har en tendens til enten å overvelde meg med kjærlighet eller forlate meg	☐	☐
133	Jeg er ikke sikker på om stemmer jeg har hørt eller ting jeg har sett er fri fantasi eller virkelighet	☐	☐
134	Jeg opplever meg selv som helt ulik til ulike tidspunkter	☐	☐
135	Jeg er redd for nære forhold	☐	☐
136	Folk betrakter meg gjerne som et stemnings-menneske	☐	☐
137	Jeg oppfører meg på måter som folk oppfatter som uventede eller skiftende	☐	☐
138	Jeg har hørt eller sett ting det ikke er noen åpenbar forklaring på	☐	☐
139	Jeg liker å leve et avvekslende liv	☐	☐
140	Jeg tror ting kan skje bare jeg tenker på det	☐	☐
141	Jeg er usikker på hva folk tenker om meg, selv om de kjenner meg svært godt	☐	☐
142	I et forhold føler jeg meg som i en felle	☐	☐
143	Det er vanskelig for meg å holde fast på min egen overbevisning når andre insisterer på sin	☐	☐
144	Jeg handler ofte på øyeblikkets innskytelse	☐	☐
145	Jeg er svært intens i mitt følelsesliv	☐	☐
146	Mine følelser svinger mellom ytterpunktene, jeg føler enten sterk glede eller intens desperasjon.	☐	☐
147	Jeg vet ikke om enkelte fornemmelser er virkelige eller om jeg bare forestiller meg dem	☐	☐
148	Mange mennesker betrakter meg som en livlig person	☐	☐
149	En del av de som kjenner meg, synes jeg er nokså aggressiv	☐	☐
150	Hører jeg om noe som er trist og leit, kan det gå sterkt inn på meg, slik at jeg føler meg helt syk i lang tid etterpå	☐	☐
151	Jeg liker forandringer, jeg trives ikke hvis den ene dagen er for lik den andre	☐	☐
152	Når jeg er ute blant folk og et eller annet spørsmål diskuteres, blir det gjerne til at jeg sitter taus og bare hører på	☐	☐
153	Folk behandler meg som en «ting»	☐	☐
154	Jeg liker å vise folk nøyaktig hvordan jeg føler	☐	☐
155	Jeg har vanskelig for å beskrive meg selv	☐	☐
156	Bortsett fra når det gjelder nære venner, er jeg temmelig reservert og tilbakeholdende	☐	☐
157	Jeg har vært i forhold hvor jeg ikke var i stand til å vite om tanker og følelser tilhørte meg selv eller den andre	☐	☐
158	I situasjoner hvor jeg egentlig burde synge ut, kan jeg bli helt stum og ikke få fram et eneste ord	☐	☐
159	Jeg gjør ting jeg synes er OK når det skjer, men som jeg senere har vanskelig for å forstå at jeg kan ha gjort.	☐	☐
160	Jeg pleier å oppbevare allting på sin faste plass, slik at jeg lett finner tingene når jeg trenger dem	☐	☐
161	Jeg har vanskelig for å holde på venner	☐	☐
162	Av og til føler jeg at jeg ikke har noen egen vilje i det hele tatt	☐	☐
163	Jeg føler jeg ikke får det jeg har behov for	☐	☐
164	Jeg kan gjøre ting som får folk til å bli helt ute av seg uten at jeg skjønner hvorfor de reagerer slik	☐	☐
165	Jeg undrer meg over hvem jeg egentlig er	☐	☐
166	Folk som virker bra til å begynne med, ender ofte opp med å skuffe meg	☐	☐

		Galt	Riktig
167	Av og til får jeg rare tanker i hodet som jeg ikke er i stand til å få vekk	☐	☐
168	Jeg kan føle det som jeg betrakter meg selv spille en rolle	☐	☐
169	Jeg har av og til en følelse av at ingen vil ha noe med meg å gjøre	☐	☐
170	Det virker som om andre får pengene til å strekke bedre til enn jeg gjør, enda de ikke har mer å rutte med	☐	☐
171	Jeg føler det av og til som om jeg lever i en tåke	☐	☐
172	Ofte er jeg ikke i stand til å si hva jeg vil gjøre i neste øyeblikk	☐	☐
173	Ofte synes det som om andre gjør allting mye bedre enn jeg selv	☐	☐
174	Jeg er usikker på meg selv som mann (kvinne)	☐	☐
175	Jeg er svært nærtakende for kritikk	☐	☐
176	For mitt temperament passer det best med et velordnet liv og en fast rutine	☐	☐
177	Det ligger nok slett ikke for meg å tenke raskt og svare kjapt	☐	☐
178	Jeg har lett for å bli ledet av andre	☐	☐

Her er en liste over ulike reaksjoner og opplevelser. Kryss av hvis disse beskrivelsene passer for deg nå eller har passet for deg før (for mer enn et halvt år siden).

179		Passer nå	Passet før	Passer ikke
	Jeg føler sterkt ubehag når jeg omgås mange mennesker på en gang, f.eks. i butikker, på gaten eller på kino	☐	☐	☐
	Jeg føler meg ofte redd når jeg reiser alene med buss, trikk eller tog	☐	☐	☐
	Jeg føler sterkt ubehag ved å spise eller drikke ute blant folk, f.eks. i kantine, på kafe eller restaurant	☐	☐	☐
	Jeg er redd for å rødme eller skjelve når folk ser på	☐	☐	☐
	Jeg er veldig redd for bestemte ting, f.eks. dyr, høyder, dypt vann, blod, å fly	☐	☐	☐
	Jeg kan plutslig bli veldig redd eller få panikk uten grunn	☐	☐	☐
	Jeg har hatt plutselige anfall med hjertebank, pustebesvær og svimmelhet	☐	☐	☐
	Andre sier jeg vasker og rydder altfor grundig	☐	☐	☐
	Jeg sjekker og kontrollerer alt for ofte, f.eks. kokeplater og låste dører	☐	☐	☐
	Ofte plages jeg av «dumme» tanker som kommer igjen og igjen	☐	☐	☐
	Jeg har hatt perioder da jeg har vært svært aktiv og snakkesalig	☐	☐	☐
	Jeg har hatt perioder da jeg har vært nedfor og samtidig hatt søvnvansker og dårlig konsentrasjonsevne	☐	☐	☐
	Jeg har av og til vært i kontakt med politiet på grunn av bråk eller slagsmål	☐	☐	☐
	Det hender at jeg føler at jeg blir påvirket av krefter utenfor meg selv	☐	☐	☐
	Jeg føler av og til at noen kan lese mine private tanker	☐	☐	☐

180 Er det i orden at du kontaktes igjen ved mulige senere tvillingundersøkelser? ☐ Ja ☐ Nei

Vennligst legg det utfylte spørreskjemaet i den vedlagte svarkonvolutten og postlegg den så snart som mulig. Porto er betalt.

Tusen takk for hjelpen

APPENDIX 2

DSM-IV-TR diagnostic criteria for paranoid, schizoid, schizotypal, antisocial, borderline, histrionic, narcissistic, avoidant, dependent and obsessive-compulsive personality disorder.

DSM-IV-TR diagnostic criteria for paranoid personality disorder

A. A pervasive distrust and suspiciousness of others such that their motives are interpreted as malevolent, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:

   1) suspects, without sufficient basis, that others are exploiting, harming or deceiving him or her
   2) is preoccupied with unjustified doubts about the loyalty or trustworthiness of friends or associates
   3) is reluctant to confide in others because of unwarranted fear that the information will be used maliciously against him or her
   4) reads hidden demeaning or threatening meaning into benign remarks or events
   5) persistently bears grudges, i.e. is unforgiving of insults, injuries, or slights
   6) perceives attacks on his or her character or reputation that are not apparent to others and is quick to react angrily or to counterattack
   7) has recurrent suspicions, without justification, regarding fidelity of spouse or sexual partner

B. Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, or any other psychotic disorder and is not due to the direct physiological effects of a general medical condition.

DSM-IV-TR diagnostic criteria for schizoid personality disorder

A. A pervasive pattern of detachment from social relationships and a restricted range of expression of emotions in interpersonal settings, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:

   1) neither desires nor enjoys close relationships, including being a part of a family
   2) almost always chooses solitary activities
   3) has little, if any, interest in having sexual experiences with another person
   4) take pleasure in few, if any, activities
   5) lacks close friends or confidants other than first-degree relatives
   6) appears indifferent to the praise or criticism of others
   7) shows emotional coldness, detachment, or flattened affectivity

B. Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, another psychotic disorder, or a pervasive developmental disorder and is not due to the direct physiological effects of a general medical condition.

DSM-IV-TR diagnostic criteria for schizotypal personality disorder

A. A pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behavior, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

   1) ideas of reference (excluding delusions of reference)
   2) odd beliefs or magical thinking that influences behavior and is inconsistent with subcultural norms (e.g. superstitiousness, belief in clairvoyance, telepathy, or "sixth sense"; in children and adolescents, bizarre fantasies or preoccupations)
   3) unusual perceptual experiences, including bodily illusions
   4) odd thinking and speech (e.g. vague, circumstantial, metaphorical, overelaborate, or stereotyped)
   5) suspiciousness or paranoid ideation
   6) inappropriate or constricted affect
   7) behavior or appearance that is odd, eccentric or peculiar
   8) lack of close friends or confidants other than first-degree relatives
   9) excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self

B. Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, another psychotic disorder, or a pervasive developmental disorder.

DSM-IV-TR diagnostic criteria for antisocial personality disorder

A. There is a pervasive pattern of disregard for and violation of the rights of others occurring since age 15 years, as indicated by three (or more) of the following:

   1) failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest
   2) deceitfulness, as indicated by repeated lying, use of aliases, or coning others for personal profit or pleasure
   3) impulsivity or failure to plan ahead
   4) irritability and aggressiveness, as indicated by repeated physical fights or assaults
   5) reckless disregard for safety for self or others
   6) consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations
   7) lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another

B. The individual is at least 18 years old
C. There is evidence for conduct disorder with onset before age 15 years
D. The occurrence of antisocial behavior is not exclusively during the course of schizophrenia or a manic episode

DSM-IV-TR diagnostic criteria for borderline personality disorder

A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as marked by five (or more) of the following:

1) frantic efforts to avoid real or imagined abandonment. Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5.
2) a pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation
3) identity disturbance: markedly and persistently unstable self-image or sense of self
4) impulcivity in at least two areas that are potentially self-damaging (e.g. spending, sex, substance-abuse, reckless driving, binge eating). Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5.
5) recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior
6) affective instability due to a marked reactivity of mood (e.g. intense episodic dysphoria, irritability, or anxiety lasting a few hours and only rarely more than a few days)
7) chronic feelings of emptiness
8) inappropriate, intense anger or difficulty controlling anger (e.g. frequent displays of temper, constant anger, recurrent physical fights)
9) transient, stress-related paranoid ideation or severe dissociative symptoms

DSM-IV-TR diagnostic criteria for histrionic personality disorder

A pervasive pattern of excessive emotionality and attention seeking, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1) is uncomfortable in situations in which he or she is not the center of attention
2) interaction with others is often characterized by inappropriate sexually seductive or provocative behavior
3) displays rapidly shifting and shallow expressions of emotions
4) consistently uses physical appearance to draw attention to self
5) has a style of speech that is excessively impressionistic and lacking in detail
6) shows self-dramatization, theatricality, and exaggerated expression of emotion
7) is suggestible, i.e., easily influenced by others or circumstances
8) considers relationships to be more intimate than they actually are

DSM-IV-TR diagnostic criteria for narcissistic personality disorder

A pervasive pattern of grandiosity (in fantasy or behavior), need for admiration, and lack of empathy, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1) has a grandiose sense of self-importance (e.g., exaggerates achievements and talents, expects to be recognized as superior without commensurate achievements)
2) is preoccupied with fantasies of unlimited success, power, brilliance, beauty, or ideal love
3) believes that he or she is "special" and unique and can only be understood by, or should associate with, other special or high-status people (or institutions)
4) requires excessive admiration
5) has a sense of entitlement, i.e., unreasonable expectations of especially favorable treatment or automatic compliance with his or her expectations
6) is interpersonally exploitative, i.e., takes advantage of others to achieve his or her own ends
7) lacks empathy: is unwilling to recognize or identify with the feelings and needs of others
8) is often envious of others or believes that others are envious of him or her
9) shows arrogant, haughty behaviors or attitudes

DSM-IV-TR diagnostic criteria for avoidant personality disorder

A pervasive pattern of social inhibition, feelings of inadequacy, and hypersensitivity to negative evaluation, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:

1) avoids occupational activities that involve significant interpersonal contact, because of fears of criticism, disapproval, or rejection
2) is unwilling to get involved with people unless certain of being liked
3) shows restraints within intimate relationships because of the fear of being ashamed or ridiculed
4) is preoccupied with being criticized or rejected in social situations
5) is inhibited in new interpersonal situations because of feelings of inadequacy
6) views self as socially inept, personally unappealing, or inferior to others
7) is usually reluctant to take personal risks or to engage in any new activities because they may be embarrassing

DSM-IV-TR diagnostic criteria for dependent personality disorder

A pervasive and excessive need to be taken care of that leads to submissive and clinging behavior and fears of separation, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1) has difficulty making everyday decisions without an excessive amount of advice and reassurance from others
2) needs others to assume responsibility for most major areas of his or her life
3) has difficulty expressing disagreement with others because of fear of loss of support or approval. Note: Do not include realistic fears of retribution.
4) has difficulty initiating project or doing things on his or her own (because of lack of self-confidence in judgments or abilities rather than a lack of motivation or energy)
5) goes to excessive lengths to obtain nurturance and support from others, to the point of volunteering to do things that are unpleasant
6) feels uncomfortable or helpless when alone because of exaggerated fears of being unable to care for himself or herself
7) urgently seeks another relationship as a source of care and support when a close relationship ends
8) is unrealistically preoccupied with fears of being left to take care of himself or herself

DSM-IV-TR diagnostic criteria for obsessive-compulsive personality disorder

A pervasive pattern of preoccupation with orderliness, perfectionism, and mental and interpersonal control, at the expense of flexibility, openness, and efficiency, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:

1) is preoccupied with details, rules, lists, order, organization, or schedules to the extent that the major point of the activity is lost
2) shows perfectionism that interferes with task completion (e.g., is unable to complete a project because his or her own overly strict standards are not met)
3) is excessively devoted to work and productivity to the exclusion of leisure activities and friendships (not accounted for by obvious economic necessity)
4) is overconscientious, scrupulous, and inflexible about matters of morality, ethics, or values (not accounted for by cultural or religious identification)
5) is unable to discard worn-out or worthless objects even when they have no sentimental value
6) is reluctant to delegate tasks or to work with others unless they submit to exactly his or her way of doing things
7) adopts a miserly spending style toward both self and others; money is viewed as something to be hoarded for future catastrophes
8) shows rigidity and stubbornness

APPENDIX 3

OpenMx example script used for analyses in Paper

```
library(polycor)
library(car)
require(psych)
require(OpenMx)
source("http://www.vipbg.vcu.edu/~vipbg/Tc24/GenEpiHelperFunctions.R")


#--- read in data ---
data<-read.csv2("09052013_SE_SPRprop_NEW_PDene.csv",
                header=T,
                na.strings=" ")


dim(data)
summary(data)
describe(data)
str(data)
head(data)

#=============================================================================
nv  <- 4        # number of variables per twin
ntv <- nv*2     # number of variables per pair
nth <- 3        # number of max thresholds
ntl <- 2    # number of min thresholds


#-- Convert variables to R's data type factor
data[,c("T2para_trunk2","T1para_trunk2")] <- mxFactor( data[,c("T2para_trunk2","T1para_trunk2")], levels=c(0:nth) )
head(data)
data[,c("T2schizt_trunk2","T1schizt_trunk2")] <- mxFactor( data[,c("T2schizt_trunk2","T1schizt_trunk2")],
levels=c(0:ntl) )
head(data)
data[,c("T2unsta_trunk2","T1unsta_trunk2")] <- mxFactor( data[,c("T2unsta_trunk2","T1unsta_trunk2")],
levels=c(0:ntl) )
head(data)
data[,c("T2SPRprop_NEW","T1SPRprop_NEW")] <- mxFactor( data[,c("T2SPRprop_NEW","T1SPRprop_NEW")], levels=c(0:nth) )
head(data)
```

```
Vars <- c("T2anti_trunk2", "T2depend_trunk2", "T2nars_trunk2", "T2para_trunk2", "T2schizo_trunk2",
"T2schizt_trunk2", "T2unsta_trunk2", "T2SPRprop_NEW", "T1anti_trunk2", "T1depend_trunk2", "T1nars_trunk2",
"T1para_trunk2", "T1schizo_trunk2", "T1schizt_trunk2", "T1unsta_trunk2", "T1SPRprop_NEW", "GROUP")

selVars <- paste(c("T2schizt_trunk2", "T2para_trunk2", "T2unsta_trunk2", "T2SPRprop_NEW", "T1schizt_trunk2",
"T1para_trunk2", "T1unsta_trunk2", "T1SPRprop_NEW"), sep="")


summary(data[, selVars])


# ------------------------------------------------------------------------------
# Subset, extract MZM, DZM, MZF, DZF and DZU data sets
# ------------------------------------------------------------------------------

mzmData     <- subset(data, GROUP==1, selVars)
mzmDataOrd  <- data.frame(mzmData)
head(mzmDataOrd)

dzmData    <- subset(data, GROUP==2, selVars)
dzmDataOrd <- data.frame(dzmData)
head(dzmDataOrd)

mzfData     <- subset(data, GROUP==3, selVars)
mzfDataOrd  <- data.frame(mzfData)
head(mzfDataOrd)

dzfData    <- subset(data, GROUP==4, selVars)
dzfDataOrd <- data.frame(dzfData)
head(dzfDataOrd)

dzuData    <- subset(data, GROUP==5, selVars)
dzuDataOrd <- data.frame(dzuData)
head(dzuDataOrd)

summary(mzmDataOrd)
summary(dzmDataOrd)
summary(mzfDataOrd)
summary(dzfDataOrd)
summary(dzuDataOrd)
```

```
#---start values, upper and lower bounds and labels for saturated model-

corVals   <- .4      # start value for correlations
lbrVal    <- -0.99   # start value for lower bounds
ubrVal    <- 0.99    # start value for upper bounds


thlab <- paste("th",  1:nth, sep=""); thlab


thstv <- matrix(c(0.61,0.80,0,0.18,0.66,0.44,0.05,0.62,0,-0.39,0.69,0.57),nrow=nth, ncol=ntv); thstv
thlbo <- matrix(c(-4,0.1,0,-4,0.1,0.2,-4,0.1,0,-4,0.1,0.2),nrow=nth, ncol=ntv); thlbo
thubo <- matrix(c(4,3,0,4,3,2,4,3,0,4,3,2),nrow=nth, ncol=ntv); thubo


thLabMZM   <- c(paste("v1t",1:nth,"MZM1",sep=""),paste("v1t",1:nth,"MZM2",sep=""), paste("v2t",1:nth,"MZM1",sep=""),
              paste("v2t",1:nth,"MZM2",sep=""),paste("v3t",1:nth,"MZM1",sep=""), paste("v3t",1:nth,"MZM2", sep=""),
              paste("v4t",1:nth,"MZM1",sep=""), paste("v4t",1:nth,"MZM2",sep=""))
thLabDZM   <- c(paste("v1t",1:nth,"DZM1",sep=""),paste("v1t",1:nth,"DZM2",sep=""), paste("v2t",1:nth,"DZM1",sep=""),
              paste("v2t",1:nth,"DZM2",sep=""),paste("v3t",1:nth,"DZM1",sep=""), paste("v3t",1:nth,"DZM2",sep=""),
              paste("v4t",1:nth,"DZM1",sep=""),paste("v4t",1:nth,"DZM2",sep=""))
thLabMZF   <- c(paste("v1t",1:nth,"MZF1",sep=""),paste("v1t",1:nth,"MZF2",sep=""), paste("v2t",1:nth,"MZF1",sep=""),
              paste("v2t",1:nth,"MZF2",sep=""),paste("v3t",1:nth,"MZF1",sep=""),paste("v3t",1:nth,"MZF2",sep=""),
              paste("v4t",1:nth,"MZF1",sep=""),paste("v4t",1:nth,"MZF2",sep=""))
thLabDZF   <- c(paste("v1t",1:nth,"DZF1",sep=""),paste("v1t",1:nth,"DZF2",sep=""), paste("v2t",1:nth,"DZF1",sep=""),
              paste("v2t",1:nth,"DZF2",sep=""), paste("v3t",1:nth,"DZF1",sep=""),paste("v3t",1:nth,"DZF2",sep=""),
              paste("v4t",1:nth,"DZF1",sep=""),paste("v4t",1:nth,"DZF2",sep=""))
thLabDZU   <- c(paste("v1t",1:nth,"DZU1",sep=""),paste("v1t",1:nth,"DZU2",sep=""),paste("v2t",1:nth,"DZU1",sep=""),
              paste("v2t",1:nth,"DZU2",sep=""),paste("v3t",1:nth,"DZU1",sep=""),paste("v3t",1:nth,"DZU2",sep=""),
              paste("v4t",1:nth,"DZU1",sep=""),paste("v4t",1:nth,"DZU2",sep=""))


# ------------------------------------------------------------------------------
# Saturated model
#-------------------------------------------------------------------------------

# Algebra for expected Mean & Threshold Matrices
meanG     <- mxMatrix( type="Zero", nrow=1, ncol=ntv, name="expMean")
```

```
thre1     <- mxMatrix( type="Full", nrow=nth, ncol=ntv, free=c(T,T,F, T,T,T, T,T,F, T,T,T), values=thstv,
                       lbound=thlbo, ubound=thubo, labels=thLabMZM, dimnames=list(thlab,selVars), name="ThreMZM" )
thre2     <- mxMatrix( type="Full", nrow=nth, ncol=ntv, free=c(T,T,F, T,T,T, T,T,F, T,T,T), values=thstv,
                       lbound=thlbo, ubound=thubo, labels=thLabDZM, dimnames=list(thlab,selVars), name="ThreDZM" )
thre3     <- mxMatrix( type="Full", nrow=nth, ncol=ntv, free=c(T,T,F, T,T,T, T,T,F, T,T,T), values=thstv,
                       lbound=thlbo, ubound=thubo, labels=thLabMZF, dimnames=list(thlab,selVars), name="ThreMZF" )
thre4     <- mxMatrix( type="Full", nrow=nth, ncol=ntv, free=c(T,T,F, T,T,T, T,T,F, T,T,T), values=thstv,
                       lbound=thlbo, ubound=thubo, labels=thLabDZF, dimnames=list(thlab,selVars), name="ThreDZF" )
thre5     <- mxMatrix( type="Full", nrow=nth, ncol=ntv, free=c(T,T,F, T,T,T, T,T,F, T,T,T), values=thstv,
                       lbound=thlbo, ubound=thubo, labels=thLabDZU, dimnames=list(thlab,selVars), name="ThreDZU" )

Inc       <- mxMatrix( type="Lower", nrow=nth, ncol=nth, free=FALSE, values=1, name="Inc" )

expThreMZM    <- mxAlgebra( expression= Inc %*% ThreMZM, name="expThreMZM" )
expThreDZM    <- mxAlgebra( expression= Inc %*% ThreDZM, name="expThreDZM" )
expThreMZF    <- mxAlgebra( expression= Inc %*% ThreMZF, name="expThreMZF" )
expThreDZF    <- mxAlgebra( expression= Inc %*% ThreDZF, name="expThreDZF" )
expThreDZU    <- mxAlgebra( expression= Inc %*% ThreDZU, name="expThreDZU" )


# Algebra for expectedVariance/Covariance Matrices
corMZM     <- mxMatrix( type="Stand", nrow=ntv, ncol=ntv, free=TRUE, values=corVals, lbound=lbrVal, ubound=ubrVal,
                        dimnames=list(selVars,selVars), name="expCorMZM" )
corDZM     <- mxMatrix( type="Stand", nrow=ntv, ncol=ntv, free=TRUE, values=corVals, lbound=lbrVal, ubound=ubrVal,
                        dimnames=list(selVars,selVars), name="expCorDZM" )
corMZF     <- mxMatrix( type="Stand", nrow=ntv, ncol=ntv, free=TRUE, values=corVals, lbound=lbrVal, ubound=ubrVal,
                        dimnames=list(selVars,selVars), name="expCorMZF" )
corDZF     <- mxMatrix( type="Stand", nrow=ntv, ncol=ntv, free=TRUE, values=corVals, lbound=lbrVal, ubound=ubrVal,
                        dimnames=list(selVars,selVars), name="expCorDZF" )
corDZU     <- mxMatrix( type="Stand", nrow=ntv, ncol=ntv, free=TRUE, values=corVals, lbound=lbrVal, ubound=ubrVal,
                        dimnames=list(selVars,selVars), name="expCorDZU" )

# Data objects for Multiple Groups
dataMZM    <- mxData( observed=mzmData, type="raw" )
dataDZM    <- mxData( observed=dzmData, type="raw" )
dataMZF    <- mxData( observed=mzfData, type="raw" )
dataDZF    <- mxData( observed=dzfData, type="raw" )
dataDZU    <- mxData( observed=dzuData, type="raw" )
```

```
# Objective objects for Multiple Groups
objMZM     <- mxFIMLObjective( covariance="expCorMZM", means="expMean", dimnames=selVars, thresholds="expThreMZM" )
objDZM     <- mxFIMLObjective( covariance="expCorDZM", means="expMean", dimnames=selVars, thresholds="expThreDZM" )
objMZF     <- mxFIMLObjective( covariance="expCorMZF", means="expMean", dimnames=selVars, thresholds="expThreMZF" )
objDZF     <- mxFIMLObjective( covariance="expCorDZF", means="expMean", dimnames=selVars, thresholds="expThreDZF" )
objDZU     <- mxFIMLObjective( covariance="expCorDZU", means="expMean", dimnames=selVars, thresholds="expThreDZU" )


# Combine Groups
pars        <- c(meanG, thre1, thre2, thre3, thre4, thre5, Inc, expThreMZM, expThreDZM, expThreMZF, expThreDZF,
                 expThreDZU)
groupMZM   <- mxModel(pars, corMZM, dataMZM, objMZM, name="MZM")
groupDZM   <- mxModel(pars, corDZM, dataDZM, objDZM, name="DZM")
groupMZF   <- mxModel(pars, corMZF, dataMZF, objMZF, name="MZF")
groupDZF   <- mxModel(pars, corDZF, dataDZF, objDZF, name="DZF")
groupDZU   <- mxModel(pars, corDZU, dataDZU, objDZU, name="DZU")

minus2ll  <- mxAlgebra( MZM.objective+ DZM.objective+MZF.objective+ DZF.objective+DZU.objective,
                       name="minus2sumloglikelihood" )
obj       <- mxAlgebraObjective( "minus2sumloglikelihood" )
ciCor     <- mxCI(c('MZM.expCorMZM','DZM.expCorDZM','MZF.expCorMZF','DZF.expCorDZF','DZU.expCorDZU'), interval=0.95)
twinSatModel   <- mxModel( "twinSat", minus2ll, obj, groupMZM, groupDZM, groupMZF, groupDZF, groupDZU, ciCor )


twinSatFit     <- mxRun( twinSatModel, intervals=F )
twinSatSumm    <- summary( twinSatFit );twinSatSumm

twinSatFit@output$matrices
twinSatFit@output$algebra


#-------------------------------------------------------------------------------------------------------------
# Tetravariate ACE Cholesky with quantitative sex differences and different thresholds for males and females
#-------------------------------------------------------------------------------------------------------------

vars     <- c("schizt_trunk2","para_trunk2","unsta_trunk2","SPRprop_NEW")

# start values and labels to enable different thresholds for males and females
thstv  <- matrix(c(0.61,0.80,0,0.18,0.66,0.44,0.05,0.62,0,-0.39,0.69,0.57),nrow=nth, ncol=ntv); thstv
thlbo  <- matrix(c(-4,0.1,0,-4,0.1,0.2,-4,0.1,0,-4,0.1,0.2),nrow=nth, ncol=ntv); thlbo
```

```
thubo  <- matrix(c(4,3,0,4,3,2,4,3,0,4,3,2),nrow=nth, ncol=ntv); thubo

thlbmzm  <- c(paste("v1t",1:nth,"MZM1",sep=""),paste("v2t",1:nth,"MZM1",sep=""),paste("v3t",1:nth,"MZM1",sep=""),
                      paste("v4t",1:nth,"MZM1",sep=""))
thlbdzm   <- c(paste("v1t",1:nth,"DZM1",sep=""),paste("v2t",1:nth,"DZM1",sep=""),paste("v3t",1:nth,"DZM1",sep=""),
                      paste("v4t",1:nth,"DZM1",sep=""))
thlbmzf   <- c(paste("v1t",1:nth,"MZF1",sep=""),paste("v2t",1:nth,"MZF1",sep=""),paste("v3t",1:nth,"MZF1",sep=""),
                      paste("v4t",1:nth,"MZF1",sep=""))
thlbdzf   <- c(paste("v1t",1:nth,"DZF1",sep=""),paste("v2t",1:nth,"DZF1",sep=""),paste("v3t",1:nth,"DZF1",sep=""),
                      paste("v4t",1:nth,"DZF1",sep=""))
thlbdzu   <- c(paste("v1t",1:nth,"DZU1",sep=""),paste("v2t",1:nth,"DZU1",sep=""),paste("v3t",1:nth,"DZU1",sep=""),
                      paste("v4t",1:nth,"DZU1",sep=""))


#--- Model parameters

# Specify a, c, and e path coefficients
PathAm     <- mxMatrix("Lower", nrow=nv, ncol=nv, free=c(T,T,T,T,T,T,T,T,T,T), values=c(0.285,0.273,0.004,
                      0.486,0.219,0.501,0.001,0.357,0.001,0.519), label=c("am11","am21","am31","am41","am22",
                      "am32","am42","am33","am43","am44"), lbound=0.001, ubound=0.99, name="am")
PathAf     <- mxMatrix("Lower", nrow=nv, ncol=nv, free=c(T,T,T,T,T,T,T,T,T,T), values=c(0.291,0.260,0.001,
                      0.406,0.208,0.122,0.001,0.087,0.000,0.434), label=c("af11","af21","af31","af41","af22",
                      "af32","af42","af33","af43","af44"), lbound=0.001, ubound=0.99, name="af")
PathCm     <- mxMatrix("Lower", nrow=nv, ncol=nv, free=c(T,T,T,T,T,T,T,T,T,T), values= c(0.470,0.012,0.073,
                      0.001,0.013,0.040,0.001,0.005,0.002,0.001), label=c("cm11","cm21","cm31","cm41","cm22",
                      "cm32","cm42","cm33","cm43","cm44"), lbound=0.001, ubound=0.99, name="cm")
PathCf     <- mxMatrix("Lower", nrow=nv, ncol=nv, free=c(T,T,T,T,T,T,T,T,T,T), values=c(0.312,0.243,0.459,
                      0.110,0.251,0.251,0.110,0.043,0.240,0.230), label=c("cf11","cf21","cf31","cf41",
                      "cf22","cf32","cf42","cf33","cf43","cf44"), lbound=0.001, ubound=0.99, name="cf")
PathEm     <- mxMatrix("Lower", nrow=nv, ncol=nv, free=c(T,T,T,T,T,T,T,T,T,T), values=c(0.834,0.528,0.338,
                      0.042,0.772,0.147,0.000,0.690,0.070,0.697), label=c("em11","em21","em31","em41","em22",
                      "em32","em42","em33","em43","em44"), lbound=0.001, ubound=0.99, name="em")
PathEf     <- mxMatrix("Lower", nrow=nv, ncol=nv, free=c(T,T,T,T,T,T,T,T,T,T), values=c(0.903,0.494,0.362,0.043,
                      0.722,0.157,0.001,0.737,0.071,0.709), label=c("ef11","ef21","ef31","ef41","ef22",
                      "ef32","ef42","ef33","ef43","ef44"), lbound=0.001, ubound=0.99, name="ef")

# ACE variance components
CovAm       <- mxAlgebra(am %*% t(am), name="Am")
CovAf       <- mxAlgebra(af %*% t(af), name="Af")
CovCm       <- mxAlgebra(cm %*% t(cm), name="Cm")
```

```
CovCf       <- mxAlgebra(cf %*% t(cf), name="Cf")
CovEm       <- mxAlgebra(em %*% t(em), name="Em")
CovEf       <- mxAlgebra(ef %*% t(ef), name="Ef")

# Calculate total variances
CovPm       <- mxAlgebra(Am+Cm+Em, name="Vm")
CovPf       <- mxAlgebra(Af+Cf+Ef, name="Vf")
matUnv      <- mxMatrix( type="Unit", nrow=nv, ncol=1, name="Unv1" )
var1        <- mxConstraint( expression=diag2vec(Vm)==Unv1, name="Var1" )
var2        <- mxConstraint( expression=diag2vec(Vf)==Unv1, name="Var2" )

# Algebras generated to hold Parameter Estimates and Derived Variance Components
#rowVars    <- rep('vars',nv)
#colVars    <- rep(c('A','C','E','SA','SC','SE'),each=nv)
#estVars    <- mxAlgebra( expression=cbind(A,C,E,A/V,C/V,E/V), dimnames=list(rowVars,colVars), name="Vars" )

# Algebra to compute standardized path estimares and variance components

matI <-       mxMatrix("Iden", nrow=nv, ncol=nv, name="I")
isdm <-       mxAlgebra(expression=solve(sqrt(I*Vm)), name="isdm")
isdf <-       mxAlgebra(expression=solve(sqrt(I*Vf)), name="isdf")

#--- Algebra to compute standardized path estimares and variance components
StandAm     <-       mxAlgebra(expression=am %*% isdm, name="stam")
StandCm     <-       mxAlgebra(expression=cm %*% isdm, name="stcm")
StandEm     <-       mxAlgebra(expression=em %*% isdm, name="stem")
h2m         <-       mxAlgebra(expression=Am/Vm,        name="h2m")
c2m         <-       mxAlgebra(expression=Cm/Vm,        name="c2m")
e2m         <-       mxAlgebra(expression=Em/Vm,        name="e2m")
StandAf     <-       mxAlgebra(expression=af %*% isdf, name="staf")
StandCf     <-       mxAlgebra(expression=cf %*% isdf, name="stcf")
StandEf     <-       mxAlgebra(expression=ef %*% isdf, name="stef")
h2f         <-       mxAlgebra(expression=Af/Vf,        name="h2f")
c2f         <-       mxAlgebra(expression=Cf/Vf,        name="c2f")
e2f         <-       mxAlgebra(expression=Ef/Vf,        name="e2f")

# Matrices & Algebra for expected MEANS
eMean1      <- mxMatrix( type="Zero", nrow=1, ncol=nv, name="Mean" )
eMean12     <- mxAlgebra( expression= cbind(Mean,Mean), name="expMean" )
```

```
# Matrices & Algebra for thresholds
Inc         <- mxMatrix("Lower", nrow=nth, ncol=nth, free=F, values=1, name="Inc")
thre1       <- mxMatrix( type="Full", nrow=nth, ncol=nv, free=c(T,T,F,T,T,T,T,F,T,T,T), values=thstv,
                         lbound=thlbo, ubound=thubo, labels=thlbmzm, dimnames=list(thlab,vars), name="ThreMZM")
thre2       <- mxMatrix( type="Full", nrow=nth, ncol=nv, free=c(T,T,F,T,T,T,T,F,T,T,T), values=thstv,
                         lbound=thlbo, ubound=thubo, labels=thlbmzm, dimnames=list(thlab,vars), name="ThreMZM" )
thre3       <- mxMatrix( type="Full", nrow=nth, ncol=nv, free=c(T,T,F,T,T,T,T,F,T,T,T), values=thstv,
                         lbound=thlbo, ubound=thubo, labels=thlbmzf, dimnames=list(thlab,vars), name="ThreMZF" )
thre4       <- mxMatrix( type="Full", nrow=nth, ncol=nv, free=c(T,T,F,T,T,T,T,F,T,T,T), values=thstv,
                         lbound=thlbo, ubound=thubo, labels=thlbmzf, dimnames=list(thlab,vars), name="ThreMZF" )
thre5       <- mxMatrix( type="Full", nrow=nth, ncol=ntv, free=c(T,T,F,T,T,T,T,F,T,T,T), values=thstv,
                         lbound=thlbo, ubound=thubo, labels=c(thlbmzf,thlbmzm), name="ThreDZU" )

# Expected thresholds
expThreMZM1     <- mxAlgebra( expression= ( Inc %*% ThreMZM ),name="expThreMZM1")
expThreMZM2     <- mxAlgebra( expression= ( Inc %*% ThreMZM ),name="expThreMZM2")
eThreMZM        <- mxAlgebra( expression= cbind( expThreMZM1,expThreMZM2 ),name="eThreMZM" )
expThreMZF1     <- mxAlgebra( expression= ( Inc %*% ThreMZF ),name="expThreMZF1")
expThreMZF2     <- mxAlgebra( expression= ( Inc %*% ThreMZF ),name="expThreMZF2")
eThreMZF        <- mxAlgebra( expression= cbind( expThreMZF1,expThreMZF2 ),name="eThreMZF" )
eThreDZU        <- mxAlgebra( expression= ( Inc %*% ThreDZU ),name="eThreDZU")


# Expected variance/covariance matrices
expCovMZM   <- mxAlgebra(expression=rbind( cbind(Am+Cm+Em, Am+Cm),
                         cbind(Am+Cm,   Am+Cm+Em)), name="expCovMZM")
expCovDZM   <- mxAlgebra(expression=rbind( cbind( Am+Cm+Em, 0.5 %x% Am+Cm),
                         cbind( 0.5 %x% Am+Cm, Am+Cm+Em)), name="expCovDZM")
expCovMZF   <- mxAlgebra(expression=rbind( cbind(Af+Cf+Ef, Af+Cf),
                         cbind(Af+Cf,   Af+Cf+Ef)), name="expCovMZF")
expCovDZF   <- mxAlgebra(expression=rbind( cbind( Af+Cf+Ef, 0.5 %x% Af+Cf),
                         cbind( 0.5 %x% Af+Cf, Af+Cf+Ef)), name="expCovDZF")
expCovDZU   <- mxAlgebra(expression=rbind( cbind( Af+Cf+Ef, 0.5 %x% (af %*% t(am))+cf %*% t(cm)),
                         cbind( 0.5 %x% (am%*%t(af))+cm%*% t(cf), Am+Cm+Em)), name="expCovDZU")

# Algebra to calculate genetic and environmental correlations
corAm       <- mxAlgebra( expression= solve(sqrt(I*Am)) %*% Am %*%solve(sqrt(I*Am)), name="rAm" )
corAf       <- mxAlgebra( expression= solve(sqrt(I*Af)) %*% Af %*%solve(sqrt(I*Af)), name="rAf" )
corCm       <- mxAlgebra( expression= solve(sqrt(I*Cm)) %*% Cm %*%solve(sqrt(I*Cm)), name="rCm" )
corCf       <- mxAlgebra( expression= solve(sqrt(I*Cf)) %*% Cf %*%solve(sqrt(I*Cf)), name="rCf" )
```

```
corEm      <- mxAlgebra( expression= solve(sqrt(I*Em)) %*% Em %*%solve(sqrt(I*Em)), name="rEm" )
corEf      <- mxAlgebra( expression= solve(sqrt(I*Ef)) %*% Ef %*%solve(sqrt(I*Ef)), name="rEf" )

# constrain A and C correlations to be equal for males and females
coreq1      <-mxConstraint(expression=rAm[2,1]==rAf[2,1], name="rAmf1")
coreq2      <-mxConstraint(expression=rAm[3,1]==rAf[3,1], name="rAmf2")
coreq3      <-mxConstraint(expression=rAm[4,1]==rAf[4,1], name="rAmf3")
coreq4      <-mxConstraint(expression=rAm[3,2]==rAf[3,2], name="rAmf4")
coreq5      <-mxConstraint(expression=rAm[4,2]==rAf[4,2], name="rAmf5")
coreq6      <-mxConstraint(expression=rAm[4,3]==rAf[4,3], name="rAmf6")
coreq7      <-mxConstraint(expression=rCm[2,1]==rCf[2,1], name="rCmf1")
coreq8      <-mxConstraint(expression=rCm[3,1]==rCf[3,1], name="rCmf2")
coreq9      <-mxConstraint(expression=rCm[4,1]==rCf[4,1], name="rCmf3")
coreq10     <-mxConstraint(expression=rCm[3,2]==rCf[3,2], name="rCmf4")
coreq11     <-mxConstraint(expression=rCm[4,2]==rCf[4,2], name="rCmf5")
coreq12     <-mxConstraint(expression=rCm[4,3]==rCf[4,3], name="rCmf6")

#E correlations allowed to vary between sexes
#coreq13    <-mxConstraint(expression=rEm[2,1]==rEf[2,1], name="rEmf1")
#coreq14    <-mxConstraint(expression=rEm[3,1]==rEf[3,1], name="rEmf2")
#coreq15    <-mxConstraint(expression=rEm[4,1]==rEf[4,1], name="rEmf3")
#coreq16    <-mxConstraint(expression=rEm[3,2]==rEf[3,2], name="rEmf4")
#coreq17    <-mxConstraint(expression=rEm[4,2]==rEf[4,2], name="rEmf5")
#coreq18    <-mxConstraint(expression=rEm[4,3]==rEf[4,3], name="rEmf6")

dataMZM     <-   mxData( observed=mzmDataOrd,"raw")
dataDZM     <-   mxData( observed=dzmDataOrd,"raw")
dataMZF     <-    mxData( observed=mzfDataOrd,"raw")
dataDZF     <-    mxData( observed=dzfDataOrd,"raw")
dataDZU     <-    mxData( observed=dzuDataOrd,"raw")

objMZM      <-   mxFIMLObjective(covariance="expCovMZM", means="expMean",dimnames=selVars, thresholds="eThreMZM")
objDZM      <-   mxFIMLObjective(covariance="expCovDZM", means="expMean",dimnames=selVars, thresholds="eThreMZM")
objMZF      <-   mxFIMLObjective(covariance="expCovMZF", means="expMean",dimnames=selVars, thresholds="eThreMZF")
objDZF      <-   mxFIMLObjective(covariance="expCovDZF", means="expMean",dimnames=selVars, thresholds="eThreMZF")
objDZU      <-   mxFIMLObjective(covariance="expCovDZU", means="expMean",dimnames=selVars, thresholds="eThreDZU")


# Combine Groups
pars        <- c( PathAm, PathAf, PathCm, PathCf, PathEm, PathEf, CovAm, CovAf, CovCm, CovCf, CovEm, CovEf, CovPm,
```

```
          CovPf, matUnv, matI, isdm, isdf, StandAm, StandCm, StandEm, h2m, c2m, e2m, StandAf, StandCf, StandEf,
          h2f, c2f, e2f, eMean1, eMean12, Inc, thre1, thre2,
          thre3, thre4, thre5, expThreMZM1, expThreMZM2, eThreMZM, expThreMZF1, expThreMZF2, eThreMZF, eThreDZU,
          corAm, corAf, corCm, corCf, corEm, corEf )
modelMZM     <- mxModel( pars, expCovMZM, dataMZM, objMZM, name="MZM" )
modelDZM     <- mxModel( pars, expCovDZM, dataDZM, objDZM, name="DZM" )
modelMZF     <- mxModel( pars, expCovMZF, dataMZF, objMZF, name="MZF" )
modelDZF     <- mxModel( pars, expCovDZF, dataDZF, objDZF, name="DZF" )
modelDZU     <- mxModel( pars, expCovDZU, dataDZU, objDZU, name="DZU" )
minus2ll     <- mxAlgebra(MZM.objective + DZM.objective + MZF.objective + DZF.objective + DZU.objective,
                          name="minus2sumll" )
obj                <-mxAlgebraObjective("minus2sumll")
#ciVC               <-mxCI(c("MZ.a", "MZ.e"))
SexLimTetraACEModel <- mxModel( "SexLimTetraAceModel", pars, modelMZM, modelDZM, modelMZF, modelDZF, modelDZU,
                                minus2ll, obj, var1, var2, coreq1, coreq2, coreq3, coreq4, coreq5, coreq6,
                                coreq7, coreq8, coreq9, coreq10, coreq11, coreq12 )
SexLimTetraACEModel <- mxOption(SexLimTetraACEModel, "CI Max Iterations", 10)

SexLimTetraACE_Fit <-mxRun(SexLimTetraACEModel, intervals=F)
SexLimTetraACE_Sum <- summary(SexLimTetraACE_Fit); SexLimTetraACE_Sum

SexLimTetraACE_Fit@output$algebras
SexLimTetraACE_Fit@output$matrices


#-----------------------------------------------------------------
# Running AE-model with quantitative sex differences
#-----------------------------------------------------------------

AESexModel <- mxModel (SexLimTetraACE_Fit, name = "AESex")
AESexModel <- omxSetParameters (AESexModel, labels=c("cm11","cm21","cm31","cm41","cm22","cm32","cm42","cm33","cm43",
                                "cm44","cf11","cf21","cf31","cf41","cf22","cf32","cf42","cf33","cf43","cf44"),
                                free=F, values=0)
AESexModel <- mxModel (AESexModel, "rCmf1", remove=T)
AESexModel <- mxModel (AESexModel, "rCmf2", remove=T)
AESexModel <- mxModel (AESexModel, "rCmf3", remove=T)
AESexModel <- mxModel (AESexModel, "rCmf4", remove=T)
AESexModel <- mxModel (AESexModel, "rCmf5", remove=T)
AESexModel <- mxModel (AESexModel, "rCmf6", remove=T)
AESexModel <- mxModel (AESexModel, "MZM.rCm", remove=T)
```

```
AESexModel <- mxModel (AESexModel, "MZM.rCf", remove=T)
AESexModel <- mxModel (AESexModel, "DZM.rCm", remove=T)
AESexModel <- mxModel (AESexModel, "DZM.rCf", remove=T)
AESexModel <- mxModel (AESexModel, "MZF.rCm", remove=T)
AESexModel <- mxModel (AESexModel, "MZF.rCf", remove=T)
AESexModel <- mxModel (AESexModel, "DZF.rCm", remove=T)
AESexModel <- mxModel (AESexModel, "DZF.rCf", remove=T)
AESexModel <- mxModel (AESexModel, "DZU.rCm", remove=T)
AESexModel <- mxModel (AESexModel, "DZU.rCf", remove=T)
AESexModel <- mxModel (AESexModel, "rCm", remove=T)
AESexModel <- mxModel (AESexModel, "rCf", remove=T)
AESexModel <- mxModel (AESexModel, "rEmf1", remove=T)
AESexModel <- mxModel (AESexModel, "rEmf2", remove=T)
AESexModel <- mxModel (AESexModel, "rEmf3", remove=T)
AESexModel <- mxModel (AESexModel, "rEmf4", remove=T)
AESexModel <- mxModel (AESexModel, "rEmf5", remove=T)
AESexModel <- mxModel (AESexModel, "rEmf6", remove=T)

AESex_Fit   <- mxRun(AESexModel, intervals=F)
AESexSumm   <- summary(AESex_Fit); AESexSumm

AESex_Fit@output$algebras


#------------------------------------------------------------------
# Running CE-model with quantitative sex differences
#------------------------------------------------------------------

CESexModel <- mxModel (SexLimTetraACE_Fit, name = "CESex")
CESexModel <- omxSetParameters (CESexModel, labels=c("am11","am21","am31","am41","am22","am32","am42","am33","am43",
                                  "am44","af11","af21","af31","af41","af22","af32","af42","af33","af43","af44"),
                                  free=F, values=0)
CESexModel <- mxModel (CESexModel, "rAmf1", remove=T)
CESexModel <- mxModel (CESexModel, "rAmf2", remove=T)
CESexModel <- mxModel (CESexModel, "rAmf3", remove=T)
CESexModel <- mxModel (CESexModel, "rAmf4", remove=T)
CESexModel <- mxModel (CESexModel, "rAmf5", remove=T)
CESexModel <- mxModel (CESexModel, "rAmf6", remove=T)
CESexModel <- mxModel (CESexModel, "MZM.rAm", remove=T)
CESexModel <- mxModel (CESexModel, "MZM.rAf", remove=T)
```

```
CESexModel <- mxModel (CESexModel, "DZM.rAm", remove=T)
CESexModel <- mxModel (CESexModel, "DZM.rAf", remove=T)
CESexModel <- mxModel (CESexModel, "MZF.rAm", remove=T)
CESexModel <- mxModel (CESexModel, "MZF.rAf", remove=T)
CESexModel <- mxModel (CESexModel, "DZF.rAm", remove=T)
CESexModel <- mxModel (CESexModel, "DZF.rAf", remove=T)
CESexModel <- mxModel (CESexModel, "DZU.rAm", remove=T)
CESexModel <- mxModel (CESexModel, "DZU.rAf", remove=T)
CESexModel <- mxModel (CESexModel, "rAm", remove=T)
CESexModel <- mxModel (CESexModel, "rAf", remove=T)
CESexModel <- mxModel (CESexModel, "rEmf1", remove=T)
CESexModel <- mxModel (CESexModel, "rEmf2", remove=T)
CESexModel <- mxModel (CESexModel, "rEmf3", remove=T)
CESexModel <- mxModel (CESexModel, "rEmf4", remove=T)
CESexModel <- mxModel (CESexModel, "rEmf5", remove=T)
CESexModel <- mxModel (CESexModel, "rEmf6", remove=T)

CESex_Fit <- mxRun(CESexModel, intervals=F)
CESexSumm  <- summary(CESex_Fit); CESexSumm

#------------------------------------------------------------------
# Running E-model with quantitative sex differences
#------------------------------------------------------------------

ESexModel <- mxModel (AESex_Fit, name = "ESex")
ESexModel <- omxSetParameters (ESexModel, labels=c("am11","am21","am31","am41","am22","am32","am42","am33","am43",
                                   "am44","af11","af21","af31","af41","af22","af32","af42","af33","af43","af44"),
                                   free=F, values=0)
ESexModel <- omxSetParameters (ESexModel, labels=c("em11","em21","em31","em41","em22","em32","em42","em33","em43",
                                   "em44","ef11","ef21","ef31","ef41","ef22","ef32","ef42","ef33","ef43","ef44"),
                                   free=T, values=.50)
ESexModel <- mxModel (ESexModel, "rAmf1", remove=T)
ESexModel <- mxModel (ESexModel, "rAmf2", remove=T)
ESexModel <- mxModel (ESexModel, "rAmf3", remove=T)
ESexModel <- mxModel (ESexModel, "rAmf4", remove=T)
ESexModel <- mxModel (ESexModel, "rAmf5", remove=T)
ESexModel <- mxModel (ESexModel, "rAmf6", remove=T)
ESexModel <- mxModel (ESexModel, "MZM.rAm", remove=T)
ESexModel <- mxModel (ESexModel, "MZM.rAf", remove=T)
ESexModel <- mxModel (ESexModel, "DZM.rAm", remove=T)
```

```
ESexModel <- mxModel (ESexModel, "DZM.rAf", remove=T)
ESexModel <- mxModel (ESexModel, "MZF.rAm", remove=T)
ESexModel <- mxModel (ESexModel, "MZF.rAf", remove=T)
ESexModel <- mxModel (ESexModel, "DZF.rAm", remove=T)
ESexModel <- mxModel (ESexModel, "DZF.rAf", remove=T)
ESexModel <- mxModel (ESexModel, "DZU.rAm", remove=T)
ESexModel <- mxModel (ESexModel, "DZU.rAf", remove=T)
ESexModel <- mxModel (ESexModel, "rAm", remove=T)
ESexModel <- mxModel (ESexModel, "rAf", remove=T)
ESexModel <- mxModel (ESexModel, "rEmf1", remove=T)
ESexModel <- mxModel (ESexModel, "rEmf2", remove=T)
ESexModel <- mxModel (ESexModel, "rEmf3", remove=T)
ESexModel <- mxModel (ESexModel, "rEmf4", remove=T)
ESexModel <- mxModel (ESexModel, "rEmf5", remove=T)
ESexModel <- mxModel (ESexModel, "rEmf6", remove=T)


ESex_Fit <- mxRun(ESexModel, intervals=F)
ESexSumm  <- summary(ESex_Fit); ESexSumm

tableFitStatistics(SexLimTetraACE_Fit, c(AESex_Fit, CESex_Fit, ESex_Fit))


#=============================================================================================
#--- No sex limitation tetravariate ACE cholesky model with different thresholds for males and females
#---------------------------------------------------------------------------------------------

#--- Model parameters

# Specify a, c, and e path coefficients
PathA     <- mxMatrix("Lower", nrow=nv, ncol=nv, free=c(T,T,T,T,T,T,T,T,T,T), values=c(0.3,0.3,0.2,0.3,0.3,0.2,
                      0.2,0.4,0.2,0.5), label=c("a11","a21","a31","a41","a22","a32","a42","a33","a43","a44"),
                      lbound=0.001, ubound=0.99, name="a")
PathC     <- mxMatrix("Lower", nrow=nv, ncol=nv, free=c(T,T,T,T,T,T,T,T,T,T), values=c(0.2,0.1,0.1,0.1,0.1,0.05,
                      0.05,0.05,0.05,0.05), label=c("c11","c21","c31","c41","c22","c32","c42","c33","c43","c44"),
                      lbound=0.001, ubound=0.99, name="c")
PathE     <- mxMatrix("Lower", nrow=nv, ncol=nv, free=c(T,T,T,T,T,T,T,T,T,T), values=c(0.5,0.5,0.3,0.3,0.4,0.2,
                      0.2,0.4,0.2,0.5), label=c("e11","e21","e31","e41","e22","e32","e42","e33","e43","e44"),
                      lbound=0.001, ubound=0.99, name="e")
```

```
# ACE variance components
CovA        <- mxAlgebra(a %*% t(a), name="A")
CovC        <- mxAlgebra(c %*% t(c), name="C")
CovE        <- mxAlgebra(e %*% t(e), name="E")

# Calculate total variances
CovP        <- mxAlgebra(A+C+E, name="V")
matUnv      <- mxMatrix( type="Unit", nrow=nv, ncol=1, name="Unv1" )
var1        <- mxConstraint( expression=diag2vec(V)==Unv1, name="Var1" )
matI        <- mxMatrix("Iden", nrow=nv, ncol=nv, name="I")
isd         <- mxAlgebra(expression=solve(sqrt(I*V)), name="isd")

# Algebras generated to hold Parameter Estimates and Derived Variance Components
StandA      <-       mxAlgebra(expression=a %*% isd, name="sta")
StandC      <-       mxAlgebra(expression=c %*% isd, name="stc")
StandE      <-       mxAlgebra(expression=e %*% isd, name="ste")
h2          <-       mxAlgebra(expression=A/V,        name="h2")
c2          <-       mxAlgebra(expression=C/V,        name="c2")
e2          <-       mxAlgebra(expression=E/V,        name="e2")

# Matrices & Algebra for expected MEANS
eMean1      <- mxMatrix( type="Zero", nrow=1, ncol=nv, name="Mean" )
eMean12     <- mxAlgebra( expression= cbind(Mean,Mean), name="expMean" )

# Matrices & Algebra for thresholds
Inc       <- mxMatrix("Lower", nrow=nth, ncol=nth, free=F, values=1, name="Inc")
thre1     <- mxMatrix( type="Full", nrow=nth, ncol=nv, free=c(T,T,F,T,T,T,T,F,T,T,T), values=thstv, lbound=thlbo,
                       ubound=thubo, labels=thlbmzm, dimnames=list(thlab,vars), name="ThreMZM")
thre2     <- mxMatrix( type="Full", nrow=nth, ncol=nv, free=c(T,T,F,T,T,T,T,F,T,T,T), values=thstv, lbound=thlbo,
                       ubound=thubo, labels=thlbmzm, dimnames=list(thlab,vars), name="ThreMZM" )
thre3     <- mxMatrix( type="Full", nrow=nth, ncol=nv, free=c(T,T,F,T,T,T,T,F,T,T,T), values=thstv, lbound=thlbo,
                       ubound=thubo, labels=thlbmzf, dimnames=list(thlab,vars), name="ThreMZF" )
thre4     <- mxMatrix( type="Full", nrow=nth, ncol=nv, free=c(T,T,F,T,T,T,T,F,T,T,T), values=thstv, lbound=thlbo,
                       ubound=thubo, labels=thlbmzf, dimnames=list(thlab,vars), name="ThreMZF" )
thre5     <- mxMatrix( type="Full", nrow=nth, ncol=ntv, free=c(T,T,F,T,T,T,T,T,F,T,T,T), values=thstv, lbound=thlbo,
                       ubound=thubo, labels=c(thlbmzf,thlbmzm), name="ThreDZU" )
# Expected thresholds
expThreMZM1    <- mxAlgebra( expression= ( Inc %*% ThreMZM ),name="expThreMZM1")
expThreMZM2    <- mxAlgebra( expression= ( Inc %*% ThreMZM ),name="expThreMZM2")
eThreMZM       <- mxAlgebra( expression= cbind( expThreMZM1,expThreMZM2 ),name="eThreMZM" )
```

```
expThreMZF1    <- mxAlgebra( expression= ( Inc %*% ThreMZF ),name="expThreMZF1")
expThreMZF2    <- mxAlgebra( expression= ( Inc %*% ThreMZF ),name="expThreMZF2")
eThreMZF       <- mxAlgebra( expression= cbind( expThreMZF1,expThreMZF2 ),name="eThreMZF" )
eThreDZU       <- mxAlgebra( expression= ( Inc %*% ThreDZU ),name="eThreDZU")

# Expected variance/covariance matrices
expCovMZM   <- mxAlgebra(expression=rbind( cbind(A+C+E, A+C),
                  cbind(A+C,   A+C+E)), name="expCovMZM")
expCovDZM   <- mxAlgebra(expression=rbind( cbind( A+C+E, 0.5 %x% A+C),
                        cbind( 0.5 %x% A+C, A+C+E)), name="expCovDZM")
expCovMZF   <- mxAlgebra(expression=rbind( cbind(A+C+E, A+C),
                  cbind(A+C,   A+C+E)), name="expCovMZF")
expCovDZF   <- mxAlgebra(expression=rbind( cbind( A+C+E, 0.5 %x% A+C),
                        cbind( 0.5 %x% A+C, A+C+E)), name="expCovDZF")
expCovDZU   <- mxAlgebra(expression=rbind( cbind( A+C+E, 0.5 %x% A+C),
                        cbind( 0.5 %x% A+C, A+C+E)), name="expCovDZU")

# Algebra to calculate genetic and environmental correlations
corA      <- mxAlgebra( expression= solve(sqrt(I*A)) %*% A %*%solve(sqrt(I*A)), name="rA" )
corC      <- mxAlgebra( expression= solve(sqrt(I*C)) %*% C %*%solve(sqrt(I*C)), name="rC" )
corE      <- mxAlgebra( expression= solve(sqrt(I*E)) %*% E %*%solve(sqrt(I*E)), name="rE" )

dataMZM    <-   mxData( observed=mzmDataOrd,"raw")
dataDZM    <-   mxData( observed=dzmDataOrd,"raw")
dataMZF       <- mxData( observed=mzfDataOrd,"raw")
dataDZF       <- mxData( observed=dzfDataOrd,"raw")
dataDZU       <- mxData( observed=dzuDataOrd,"raw")

objMZM      <-   mxFIMLObjective(covariance="expCovMZM", means="expMean",dimnames=selVars, thresholds="eThreMZM")
objDZM      <-   mxFIMLObjective(covariance="expCovDZM", means="expMean",dimnames=selVars, thresholds="eThreMZM")
objMZF      <-   mxFIMLObjective(covariance="expCovMZF", means="expMean",dimnames=selVars, thresholds="eThreMZF")
objDZF      <-   mxFIMLObjective(covariance="expCovDZF", means="expMean",dimnames=selVars, thresholds="eThreMZF")
objDZU      <-   mxFIMLObjective(covariance="expCovDZU", means="expMean",dimnames=selVars, thresholds="eThreDZU")


# Combine Groups
pars  <- c( PathA, PathC, PathE, CovA, CovC, CovE, CovP, matUnv, matI, isd, StandA, StandC, StandE, h2, c2, e2,
           eMean1, eMean12, Inc, thre1, thre2, thre3, thre4, thre5, expThreMZM1, expThreMZM2, eThreMZM,
           expThreMZF1, expThreMZF2, eThreMZF, eThreDZU, corA, corC, corE )
modelMZM     <- mxModel( pars, expCovMZM, dataMZM, objMZM, name="MZM" )
```

```
modelDZM     <- mxModel( pars, expCovDZM, dataDZM, objDZM, name="DZM" )
modelMZF     <- mxModel( pars, expCovMZF, dataMZF, objMZF, name="MZF" )
modelDZF     <- mxModel( pars, expCovDZF, dataDZF, objDZF, name="DZF" )
modelDZU     <- mxModel( pars, expCovDZU, dataDZU, objDZU, name="DZU" )
minus2ll     <- mxAlgebra(MZM.objective + DZM.objective + MZF.objective + DZF.objective + DZU.objective,
name="minus2sumll" )
obj                    <-mxAlgebraObjective("minus2sumll")
ciVC                   <-mxCI(c("rA", "rE"))
NoSexTetraACEModel     <- mxModel( "NoSexTetraAceModel", pars, modelMZM, modelDZM, modelMZF, modelDZF, modelDZU,
                            minus2ll, obj, var1, ciVC )
NoSexTetraACEModel     <- mxOption(NoSexTetraACEModel, "CI Max Iterations", 10)

NoSexTetraACE_Fit <-mxRun(NoSexTetraACEModel, intervals=F)
NoSexTetraACE_Sum <- summary(NoSexTetraACE_Fit); NoSexTetraACE_Sum

NoSexTetraACE_Fit@output$algebras
NoSexTetraACE_Fit@output$matrices

#------------------------------------------------------------------
# Running AE-model no sex lim
#------------------------------------------------------------------

AEModel <- mxModel (NoSexTetraACE_Fit, name = "AE")
AEModel <- omxSetParameters (AEModel, labels=c("c11","c21","c31","c41","c22","c32","c42","c33","c43","c44"), free=F,
                                 values=0)
AEModel <- omxSetParameters (AEModel, labels=c("a11","a21","a31","a41","a22","a32","a42","a33","a43","a44"), free=T,
                                 values=c(0.4,0.4,0.2,0.4,0.3,0.5,0.2,0.2,0.15,0.5))
AEModel <- mxModel (AEModel, "rC", remove=T)
AEModel <- mxModel (AEModel, "MZM.rC", remove=T)
AEModel <- mxModel (AEModel, "DZM.rC", remove=T)
AEModel <- mxModel (AEModel, "MZF.rC", remove=T)
AEModel <- mxModel (AEModel, "DZF.rC", remove=T)
AEModel <- mxModel (AEModel, "DZU.rC", remove=T)

AE_Fit <- mxRun(AEModel, intervals=T)
AESumm  <- summary(AE_Fit); AESumm

AE_Fit@output$algebras
```

```
#---------------------------------------------------------------------
# Running CE-model no sex lim
#---------------------------------------------------------------------

CEModel <- mxModel (NoSexTetraACE_Fit, name = "CE")
CEModel <- omxSetParameters (CEModel, labels=c("a11","a21","a31","a41","a22","a32","a42","a33","a43","a44"), free=F,
                             values=0)
CEModel <- mxModel (CEModel, "rA", remove=T)
CEModel <- mxModel (CEModel, "MZM.rA", remove=T)
CEModel <- mxModel (CEModel, "DZM.rA", remove=T)
CEModel <- mxModel (CEModel, "MZF.rA", remove=T)
CEModel <- mxModel (CEModel, "DZF.rA", remove=T)
CEModel <- mxModel (CEModel, "DZU.rA", remove=T)

CE_Fit <- mxRun(CEModel, intervals=F)
CESumm  <- summary(CE_Fit); CESumm

tableFitStatistics(NoSexTetraACE_Fit, c(AE_Fit, CE_Fit))

#---------------------------------------------------------------------
# Running E-model no sex lim
#---------------------------------------------------------------------

E_Model <- mxModel (AE_Fit, name = "E_")
E_Model <- omxSetParameters (E_Model, labels=c("a11","a21","a31","a41","a22","a32","a42","a33","a43","a44"),
                             free=F, values=0)
E_Model <- omxSetParameters (E_Model, labels=c("e11","e21","e31","e41","e22","e32","e42","e33","e43","e44"),
                             free=T, values=.40)
E_Model <- mxModel (E_Model, "rA", remove=T)
E_Model <- mxModel (E_Model, "MZM.rA", remove=T)
E_Model <- mxModel (E_Model, "DZM.rA", remove=T)
E_Model <- mxModel (E_Model, "MZF.rA", remove=T)
E_Model <- mxModel (E_Model, "DZF.rA", remove=T)
E_Model <- mxModel (E_Model, "DZU.rA", remove=T)

E_Fit <- mxRun(E_Model, intervals=F)
ESumm  <- summary(E_Fit); ESumm


tableFitStatistics(SexLimTetraACE_Fit, c(AESex_Fit, CESex_Fit, ESex_Fit, NoSexTetraACE_Fit, AE_Fit, CE_Fit, E_Fit))
```